Case Report

How a mild influenza B infection can kill: A case of pulmonary hemorrhage

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ABSTRACT

Viral influenza is a seasonal infection associated with significant morbidity and mortality. Rapidly fatal hemorrhagic pneumonia has been described in previously healthy individuals with β-hemolytic Streptococcus pneumoniae in a small series of patients, but it is not common in patients coinfected with influenza B and β-hemolytic Streptococcus, particularly since influenza B is considered less pathogenic than influenza A. However, despite being uncommon, this cofection seems to be associated with high morbidity and mortality, particularly in healthy individuals. We present a case of a 46-year-old previously healthy white woman presenting with 4 days of shortness of breath, sore throat, subjective fevers, and nonproductive cough with rapidly fatal hemorrhagic pneumonia confirmed to have Group A β-hemolytic Streptococcus and influenza B coinfeciton. On admission, she had a temperature of 103°F, room air oxygen saturation of 95%, a positive nasal swab for influenza B, and negative rapid strep test. Initial chest radiograph showed increased bibasilar interstitial markings. She was admitted to a regular floor and started on oseltamivir. Preliminary throat culture was positive for Group A β-hemolytic Streptococcus and penicillin V was started. Respiratory status deteriorated requiring intubation and transfer to Intensive Care Unit. Subsequently, copious bleeding was noted in her endotracheal tube. A bedside bronchoscopy with bronchoalveolar lavage revealed a hemorrhagic pneumonitis. Despite aggressive efforts, she developed shock, arrested, and died Western District Office of the Chief Medical Examiner, Roanoke, VA, USA postadmission. Blood cultures, bronchoalveolar lavage, and postmortem pulmonary tissue grew Group A β-hemolytic Streptococcus, only resistant to erythromycin.

KEY WORDS: Hemorrhage, influenza, pulmonary

INTRODUCTION

Bacterial superinfection with Group A β-hemolytic Streptococcus in healthy individuals is a rare occurrence that can follow an influenza infection. Even in milder forms of influenza B, this association can lead to severe morbidity and mortality. Not uncommonly, these cases present with severe pulmonary hemorrhage, which can mislead the treating physician to consider alternative pathologies. We present a case that illustrates this association and discusses the possible pathophysiology behind it.

CASE REPORT

A 46-year-old white woman, previously healthy, presented to the emergency department reporting shortness of breath, sore throat, myalgias, subjective fevers, chills, and nonproductive cough. Her symptoms had started four days before presentation, after cleaning an abandoned trailer with her family. The patient’s son had thereafter been diagnosed with strep throat, and her daughter was hospitalized with pneumonia and respiratory failure.

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On admission, the patient had a temperature of 103°F; she was tachycardic and had bilateral wheezes. An erythematous rash was present on her face sparing the periorbital areas and nasolabial folds, extending to her upper neck. Initial laboratory workup was unremarkable except for positive nasal swab for influenza B and with a negative rapid strep test. Her initial white blood count was 6.6 K/µL. Initial chest roentgenogram (CXR) only showed increased bibasilar interstitial markings. Her vaccination status was not available and could not be verified. The patient was admitted to a regular floor on droplet precautions, and oseltamivir was initiated. Initial oxygen saturations were above 95% on room air, but within a few hours, oxygen requirements started increasing and scant hemoptysis developed. A throat swab was positive for Group A β-hemolytic Streptococcus and penicillin V was initiated. Repeat CXR showed [Figure 1] developing bilateral effusions. Echocardiography demonstrated an ejection fraction of 60%–65% with mildly enlarged right ventricle and reduced right systolic function.

The patient’s respiratory compromise progressed, requiring intubation and transfer to the Intensive Care Unit (ICU) approximately 24 hours postadmission. Subsequently, copious amounts of bright red blood were noted in the endotracheal tube, and her oxygenation deteriorated requiring increasing oxygen supplementation (FiO2) and high levels of positive end-expiratory pressure. Eventually, she developed hemodynamic shock despite aggressive fluid resuscitation and required placement of central venous access, vasopressor support, along with stress dose steroids, and broad-spectrum antibiotics including vancomycin and piperacillin-tazobactam. Infectious diseases consult suggested workup for hantavirus infection; however, serological tests came back negative.

Due to unrelenting hemoptysis and worsening gas exchange, [Figure 2] emergent bedside bronchoscopy was performed along with bronchoalveolar lavage that was consistent with a hemorrhagic pneumonitis. Serial bronchoalveolar lavages could not be performed secondary to elevated peak airway pressures throughout the procedure and the patient’s instability. Her clinical course was also complicated by anion gap metabolic acidosis, acute kidney injury, pancytopenia (white blood count dropped to 1.1 K/µL), and disseminated intravascular coagulopathy. HIV testing was negative. Immunoglobulin levels A, G, and M 24 hours postadmissions were markedly depressed.

Despite aggressive efforts including the trial of multiple modes of mechanical ventilation including volume control, pressure control, bilevel, use of inhaled nitric oxide, paralytics, and intravenous methylene blue, the patient remained hypoxemic and in refractory shock. Extracorporeal membrane oxygenation was not an option given her pulmonary hemorrhage and coagulopathy. Subsequently, she went into cardiovascular arrest and was pronounced dead approximately 48 hours postadmission. Notably, the patient’s daughter who had also been diagnosed with influenza and superimposed bacterial pneumonia died several hours earlier secondary to multiorgan failure. Blood cultures, tracheal aspirate, and bronchoalveolar lavage all grew Group A β-hemolytic Streptococcus that was pansensitive except to erythromycin.

Postmortem examination was performed and revealed the extensive presence of Group A β-hemolytic Streptococcus in the patient’s pulmonary tissue and in blood [Figures 3 and 4]. No local capabilities for further analysis of the influenza B strain were available to determine the virulent subtype.

**DISCUSSION**

Viral influenza is a seasonal infection associated with significant morbidity and mortality. Annual vaccination is the mainstay of prevention. In healthy individuals, spontaneous resolution is the usual pattern. Prompt administration of antiviral medications has been shown to possibly reduce complications of acute influenza that include pulmonary, cardiovascular, and rarely neuromuscular pathology.\(^{[1]}\)

Of the different strains, influenza A is usually thought to be more severe and accounts for most hospitalizations and deaths, while influenza B is considered less pathogenic, causing usually a mild illness in healthy individuals. Poor prognosis with influenza B is more of a concern in vulnerable populations such as children and immunocompromised patients.

While influenza virus can cause primary viral pneumonia, secondary bacterial pneumonia complicating primary influenza infection has also been reported. The most common pathogens are Streptococcus pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, and Haemophilus influenzae.\(^{[3]}\) Unusual pathogens are Aspergillus, Legionella pneumophila, Chlamydia pneumoniae, and Streptococcus β-hemolytic.\(^{[1]}\)

Group A β-hemolytic Streptococcus, also known as Streptococcus pyogenes, is a known pathogen that can cause a variety of diseases that range from cellulitis to necrotizing fasciitis, pneumonia to bacteremia, and streptococcal toxic shock syndrome.\(^{[3]}\)

Rapidly fatal hemorrhagic pneumonia has been described in previously healthy individuals infected with S. pyogenes. In a small series in Rome, Italy, three patients had acute onset of shortness of breath, hemoptysis, and fever, rapidly developing acute respiratory failure requiring ventilator support.\(^{[4]}\) All three patients died of massive pulmonary hemorrhage less than 12 hours after the onset of their symptoms despite aggressive supportive care. Autopsy results confirmed the presence of S. pyogenes emm gene in lung tissue, which was also detected in blood and
bronchoalveolar lavage cultures. There was no report of viral prodrome in any of the patients that preceded the onset of the respiratory symptoms.

While the association between influenza and *S. pneumoniae* has been described and is the most studied pair in regards to influenza and bacterial coinfections, coinfection with *S. pyogenes* is thought to be uncommon.[2,5]

In a case series in the UK, 19 patients developed invasive *S. pyogenes*, with 14 cases having viral prodrome for a mean of 6 days before hospitalization. Influenza B was detected in four cases, all previously healthy, three of which died within 48 h of admission. The fourth case survived after a long stay in ICU and prolonged overall hospitalization.[3]

Coinfection of influenza B and streptococci has also been described in another series of three previously healthy women. After primary influenza B infection, two had cultures positive for *S. pyogenes*, one of them died, and the third one tested positive for *S. pneumoniae*. All patients received antiviral therapy along with antibiotics. Both cases of coinfection with influenza B and *S. pyogenes* also had known sick contacts. The only fatality in this case series occurred 18 days postadmission, after the patient's hospital course had been complicated by pulmonary hemorrhage and refractory shock. Bronchoscopy did not reveal active bleeding unlike in our patient who had active bleeding during bronchoscopy.[2] Table 1 highlights the above-discussed cases of coinfections including our patient and her daughter. In cases where the *S. pyogenes* bacteria was further analyzed, the emm gene found in st1.0 strain was thought to be responsible for the morbidity and mortality associated with the bacterial infection. The emm gene was also found in st89.0 strain in one of the younger patients of the UK case series who died within 24 hours of admission. The influenza B subtype was not determined in any of the cases.[2-4]
The interaction between influenza viruses and bacterial superinfections seems to be based on complex relations involving the co-infecting pathogens and the host. Although the exact mechanisms involving influenza B infection with *S. pyogenes* remain unclear, studies of coinfectioned patients have given rise to some theories in this regard. It is thought that *S. pneumoniae* usually reaches the lung and causes pneumonia by extension from the upper respiratory tract particularly the posterior nasopharynx. The host's immune mechanisms and physical barriers usually prevent the extension of the bacteria. A “viral-bacterial synergism” has been proposed theorizing that the initial viral infection can damage the epithelial lining exposing the basement membrane and extracellular matrix of the lung allowing subsequent bacterial pathogens to adhere. Second, and possibly, in addition, there is immune system dysfunction that compromises local immunity at potential sites of infection. Although there is an inflammatory response with activation of neutrophils and macrophages to combat infection, these have alterations in function and thus are ineffective at bacterial clearance.[5] Respiratory mucosal disruption, surfactant damage, ciliary dysfunction, and the flowing of inflammatory substances within the airways interfere with gas exchange, leading to impaired oxygenation, bacterial proliferation, and airway obstruction.[6] Although these changes are poorly tolerated in patients with pathologies such as chronic bronchitis, the immune response that occurs with this co-pathogenesis seems to be virulent enough to cause respiratory compromise even in healthy individuals. In fact, viral infection depletes the host's own immunity allowing bacterial superinfection. Once this occurs, viral load increases in patients while bacteria continues to dramatically proliferate, overwhelming the patient's own immune system that otherwise can often clear the virus, but unfortunately cannot contain the bacterial growth.[6]

It is thought that this does not occur if the bacterial infection precedes the viral exposure since the immune system is stimulated by the bacteria allowing rapid clearance of viral superinfection and less morbidity and mortality. Limited studies in animal models seem to suggest that the relationship between viral and bacterial infections could be bidirectional and synergistic, no matter what the nature of the inciting infection was, but this area is still insufficiently explored.[6]

**CONCLUSION**

Coinfection with influenza B and *S. pyogenes* is an uncommon occurrence but is associated with high morbidity and mortality, even in healthy individuals. The development of massive pulmonary hemorrhage is common and carries very high mortality. Therefore, patients with influenza B should not be dismissed as having “more benign influenza disease”. This supports the practice of checking for bacterial pneumonia in all patients admitted for influenza. However, whether antiviral therapy should be started empirically or if it would alter the prognosis is still unclear. Our case also raises the issue of whether the time of presentation or initiation of aggressive therapy could potentially alter the disease course, noticing that review of the literature indicates that hemorrhagic pneumonia in *S. pyogenes* is of acute onset and rapid fatal progression. Having a high index of suspicion could potentially help identify patients that may benefit from earlier and more aggressive care. In addition, further studies to determine the exact mechanism of co-pathogenesis in influenza B and *S. pyogenes* infection could open the door to new therapeutic modalities, hoping to improve prognosis in this specific patient population. On the other hand, prevention is also key, hence the importance of recommending the yearly influenza vaccine to not only reduce the spreading of the virus but also reduce the severity of the associated illness if it develops.

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**Conflicts of interest**

There are no conflicts of interest.

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