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CASE REPORT

Severe Influenza Pneumonia Complicated with Bacterial Coinfection in a Healthy Young Man: A Case Report.

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Abstract

Influenza is a contagious viral respiratory infection of significant public health concern given its association with recurring global pandemics and substantial disease burden worldwide. It typically causes an abrupt-onset febrile illness with cough, rhinitis, sore throat and other constitutional symptoms. With increased awareness of vaccination and better treatment strategies, influenza is often uncomplicated and self-limiting in majority of the healthy individuals. However, there are various factors which can increase the susceptibility of the host to severe infection. This report aims to describe a case of severe influenza pneumonia in a healthy young man and to highlight a coinfection with an unexpected opportunistic microorganism, *Burkholderia multivorans*.

Keywords: *Burkholderia multivorans; influenza A H1N1/2009; iron deficiency anaemia; pneumonia.*

Introduction

Influenza, or commonly called 'flu', is an acute respiratory infection which can arise as seasonal epidemics in temperate regions, as a pandemic when a novel influenza virus emerges or occurs year-round in some tropical countries [1]. Clinically relevant influenza illness in human is caused by influenza virus type A and B, and the transmission occurs via respiratory droplets or aerosols [2]. The clinical spectrum of influenza can range from a mild upper respiratory tract infection to a severe disease with various pulmonary and extra-pulmonary complications [3]. Established risk factors which are associated with severe outcomes of the infection (hospitalization, admission to intensive care unit, death) include age less than five years or more than 65 years, immunocompromised state, pregnancy, obesity and pre-existing medical conditions (chronic lung diseases, cardiac diseases and diabetes mellitus) [4]. However, evidence had indicated that fatal influenza pneumonia remains a threat to healthy young adults, particularly in the setting of a pandemic [5,6,7].

Case report

A 20-year-old man, previously fit and well, presented with sudden onset of high fever, intermittent headache, rhinorrhoea and productive cough with greenish sputum for four days. He had recently commenced his training in the Air Force Academy and shared living spaces with a number of trainees in the facility. Otherwise, there was no history of jungle trekking, water activities, recent travel, tobacco smoking, or any high-risk behaviour. He completed his COVID-19 vaccination but did not receive any influenza vaccine. Despite taking some medications from the military clinic, his fever persisted and the cough worsened alongside poor appetite and excessive fatigue. At the same time, several other trainees were also sick with similar symptoms. On day four of his illness, he developed progressively worsening shortness of breath and was brought to the hospital.

Upon arrival to emergency department, he remained alert but was tachypnoeic with a respiratory rate of 28 breaths/minute and an oxygen saturation of 80% at room air. His temperature was 39.9^{o}C, pulse rate was 98 beats/minute, and blood pressure was 104/67 mmHg. Chest examination revealed crackles at the right lung. Examination of other organ systems was unremarkable. Chest radiograph showed patchy consolidations in both lungs suggestive of active infection (Figure 1). Initiated on intravenous fluid and oxygen therapy, he was promptly transferred to intensive care unit (ICU). His condition continued to deteriorate and within several hours following ICU admission, he was ventilated due to severe respiratory distress and respiratory failure.

Further evaluation in ICU revealed several small abrasion wounds at his knuckles and knees which he sustained during his physical training. There was no pallor, jaundice, skin rashes, bleeding tendency, peripheral oedema, lymphadenopathy, or hepatosplenomegaly. Additional lung ultrasound scan demonstrated minimal right pleural effusion with consolidative changes at the left basal region. Cardiac assessment was essentially normal. The clinical picture was consistent with severe pneumonia. Suspected influenza, possibly complicated with a concurrent bacterial infection, Oseltamivir was commenced alongside empirical antibiotics.

His laboratory investigations showed elevated C-reactive protein (CRP 212 mg/L), leucocytosis (total white cell count, TWBC 13.8 x 10^{9}/L), hypochromic microcytic anaemia (haemoglobin 9.5 g/dL, mean corpuscular volume 77.3 fl, mean corpuscular haemoglobin 24.2 pg), low serum iron 3.1 umol/L, elevated serum ferritin 734.1 ug/L, raised transaminases (alanine transaminase 214.4 U/L, aspartate transaminase 525 U/L) and elevated creatine kinase (CK 9187 U/L). His platelet count, renal profile, blood glucose, serum bilirubin, alkaline phosphatase, and serum lactate were normal.

The respiratory panel rapid polymerase chain reaction (PCR) test was performed on the nasopharyngeal swab specimen and it was positive for influenza A H1N1/2009, confirming the diagnosis of Influenza. Other viruses including SARS-CoV-2 and atypical pneumonia pathogens were not detected. Sputum culture grew *Burkholderia multivorans* indicating a bacterial coinfection. The isolates were susceptible to ceftazidime and trimethoprim-sulfamethoxazole. The leptospiral PCR and serology, blood and urine cultures were negative. Human immunodeficiency virus and chronic viral hepatitis screening were non-reactive.

His clinical condition improved following treatment. His fever settled and the ventilator support was weaned off after three days in ICU. He completed Oseltamivir 75mg twice daily for five days. The antibiotic was adjusted to intravenous ceftazidime 2g three times daily after obtaining a positive sputum culture and was continued for seven days. A repeat chest radiograph on day 9 of admission showed marked improvement with resolution of the radiographic abnormalities (Figure 2). In view of the raised CK level which was likely related to virus-induced muscle injury, the renal function was closely monitored and was normal throughout the hospital stay. Subsequent CK measurement demonstrated a decreasing trend (1949 U/L on day 5 and 491 U/L on day 9 of admission). The CRP and transaminases also declined gradually and the TWBC normalized. Besides having some residual cough, he recovered well and was discharged after 11 days of hospitalization. A follow-up in specialist clinic two weeks after discharge revealed normalization of liver function and improvement of haemoglobin level to 10.3 g/dL with haematinics. He was allowed to perform light duties in the Academy and monitoring of the haemoglobin level would be continued in the nearest healthcare facility.

Discussion

Despite being previously healthy, this young Air Force recruit had developed severe influenza infection complicated with pneumonia, bacterial coinfection, myositis, and hepatitis. Living in a crowded environment coupled with stress from vigorous training, and possibly having undiagnosed iron deficiency anaemia (IDA) might have increased his susceptibility to severe influenza. Contagious diseases can spread more easily in a dense living space with close contact. Evidence from a study in the army camp had indicated that overcrowding appeared to impact the disease severity with a five-fold increase in the risk of influenza complicated with pneumonia [8]. Interestingly, it has also been noted that febrile respiratory infections among military recruits are frequently associated with multiple pathogens which could contribute to a more fulminant disease [9]. Furthermore, it is evident that heavy intensified exercise can lead to transient immune dysfunction and increased risk of acute respiratory infection [10]. In children, IDA has been recognized as a predictor for severe influenza [11]. As iron plays a crucial role in regulating the immune system, particularly in the proliferation of the lymphocytes, its deficiency may impair the immune response against the infection [12]. However, the interpretation of the iron study during a state of inflammation can be challenging and hence, impacting its diagnostic value. Shen et al had demonstrated that low serum iron was a common laboratory finding in patients with influenza H1N1 infection as it was noted in 92.9% of their studied subjects [13]. The inflammation itself can result in low serum iron by affecting its transport and distribution in the body as well as its absorption from the intestine [14]. A low serum ferritin is indicative of IDA, but being an acute phase protein, the level of serum ferritin is often elevated in the presence of inflammation and this may possibly mask any underlying IDA [14]. Hence, a follow-up with repeat blood counts and iron study should be

carried out in this patient after the resolution of the inflammation.

Pneumonia is a major complication of severe influenza and it can be caused by just the virus itself or present as a coinfection with other pathogens. Primary viral pneumonitis occurs during the acute phase of influenza illness following the onset of typical flu symptoms, with the patient developing increasing dyspnoea and may progress rapidly to acute respiratory distress syndrome necessitating ICU care and ventilatory support [15,16]. The predominant radiological abnormalities in influenza pneumonia are ground glass opacities, consolidations or a combination of both and the involvement is often bilateral [7,17]. A timely diagnosis of influenza is crucial. The reverse-transcription polymerase chain reaction (RT-PCR) remains a reliable and the most applicable diagnostic tool in clinical setting [18]. Antiviral therapy should be initiated as soon as possible once influenza is suspected in high risk patients or in severe disease and the standard treatment is a course of neuraminidase inhibitor of no less than five days [18].

Concomitant viral-bacterial pneumonia is not uncommon and could attribute to approximately one in four influenza deaths [19]. Evaluation of the autopsy lung specimens from 77 fatal cases of influenza A H1N1 infection in 2009 pandemic revealed that 29% of the subjects had concurrent bacterial infection, with *Streptococcus pneumoniae*, *Streptococcus pyogenes,* and *Staphylococcus aureus* being the main pathogens identified [20]. The complexed synergistic interplay between the influenza virus and the bacteria often leads to a severe infection. The viruses can damage the epithelial lining of the respiratory tract and impair the mucociliary clearance, allowing the bacteria to gain access to the binding sites, and the viral neuraminidase will facilitate bacterial adhesion by cleavage of the sialic acid on the cell surface [21]. In addition, the viral-bacterial interaction can trigger an aberrant immune response which further contributes to profound inflammation and cellular dysfunction [19,21]. A definitive diagnosis of a bacterial coinfection would require determination of the pathogens by cultures or PCR. There are no specific clinical characteristics, radiological features, or blood biomarkers which can accurately differentiate an isolated primary influenza pneumonia from one which is complicated with a concurrent bacterial infection [22]. Hence, it is important to consider a bacterial coinfection in severe influenza pneumonia, particularly in patients with respiratory failure and sepsis [21]. Cultures and PCR should be carried out and empirical antibiotics are administered early to improve patient outcome [21].

In our patient, an unusual coinfecting bacterial species was isolated. *Burkholderia multivorans* belongs to a group of Gram-negative opportunistic pathogens, *Burkholderia cepacia* complex (BCC), which is widely distributed in the soil and the natural aquatic environment [23]. *B. multivorans* rarely poses medical risk to healthy immunocompetent individuals. However, it is a frequent colonizer of the pathological lungs in cystic fibrosis (CF) and can cause serious respiratory infections in patients with CF, chronic granulomatous disease, and in immunocompromised individuals [24]. Evidence had revealed that influenza virus can alter the function of both innate and adaptive immune systems, hence is capable of inducing an immune-suppressive state in healthy adults [25]. In the susceptible hosts, *B. multivorans* infection can lead to 'Cepacia syndrome', a potentially fatal fulminant necrotizing pneumonia associated with septicaemia [26]. Besides the respiratory disease, central line-associated bloodstream infections and meningitis have also been reported [27]. Acquisition of the *B. multivorans* is either from the environment or from the healthcare facilities and inter-patient transmission among CF patients has been recognized [23]. *Nosocomial* outbreaks can be associated with contamination of the pharmaceutical products or medical devices [28]. Our patient most likely came into contact with *B. multivorans* in the soils during his training sessions. In terms of treatment, Ceftazidime and

trimethoprim-sulfamethoxazole remain the antibiotics of choice as the therapeutic options for *B. multivorans* are limited given its intrinsic resistance towards multiple antimicrobials [27,29].

Conclusion

Severe influenza illness is associated with significantly increased morbidity and mortality. Constant influenza surveillance is pivotal and vaccination remains an important preventive measure for severe disease. Determination of a concurrent bacterial infection is proven challenging with unusual pathogens continue to emerge as culprits. Maintaining a high index of suspicion regarding influenza-bacterial coinfection in clinical practice coupled with early testing and prompt treatment would be appropriate strategies to improve patient outcomes.

Conflict of Interest and financial disclosures
None

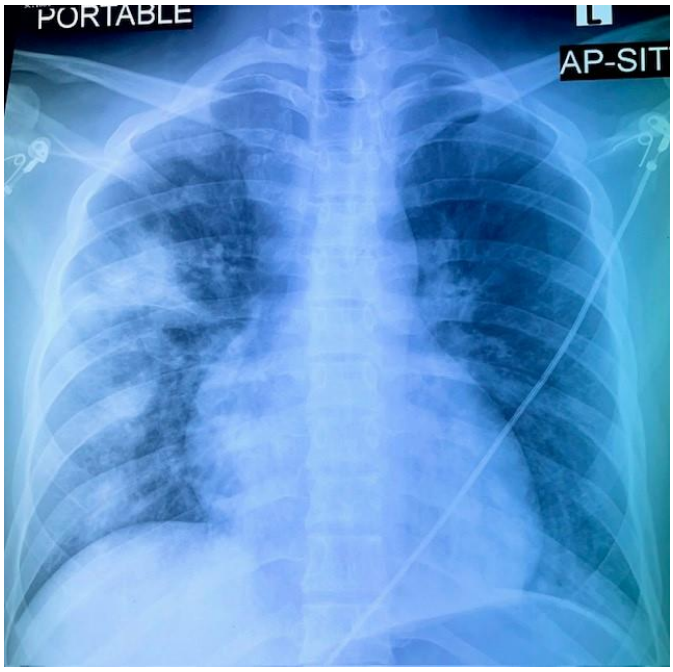

Figure 1. Chest radiograph on admission showing patchy consolidations at the upper, mid and lower zones of the right lung and mid zone of the left lung.

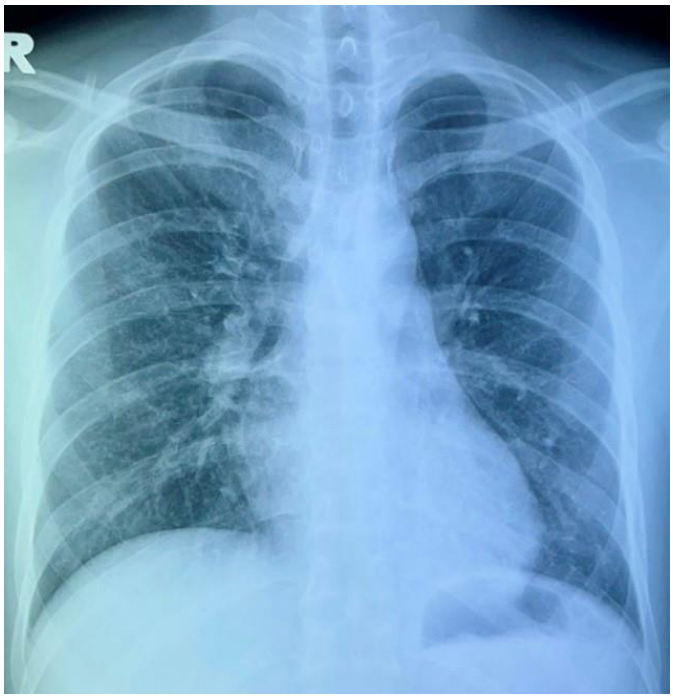

Figure 2. A repeat chest radiograph on day 9 of admission showing resolution of the consolidations.

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