CASE REPORT

Influenza A-associated Bronchospastic Pneumonia: A Case-based Review.

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Abstract

Pneumonia is the commonest influenza-associated respiratory complication in adults. The clinical presentation varies from mild to severe and may be complicated by secondary bacterial co-infection. Influenza can affect different areas of the respiratory tract (upper, lower, respiratory zones), giving rise to mixed symptoms and signs. This is due to the distribution of different types of sialic acid receptors within the respiratory tract, acting as viral binding sites with relative subtype specificity.

We present a case of an 87-year-old woman with multiple co-morbidities, diagnosed with primary influenza A pneumonia upon her return from Umrah. She had a prominent wheeze and was hypoxic, requiring bronchodilators with supplemental oxygen. Additional therapy consisted of oseltamivir, with antibiotic cover. She required a protracted hospital stay prior to recovery. This article will discuss the pathophysiology of influenza-associated respiratory complications, chest x-ray changes in influenza and related viral pneumonias, secondary bacterial co-infection management and the evolution of specific influenza antiviral therapy. We will also briefly touch upon novel antiviral agents awaiting clinical evaluation.

Keywords: B*aloxavir; favipiravir; influenza-associated complications; neuraminidase inhibitors; primary viral pneumonia; secondary bacterial pneumonia; sialic acid receptors; ventilation-perfusion mismatch.*

Introduction

Influenza, commonly known as 'flu', is a common viral respiratory infection. It is caused by infection with the influenza virus, which is a negative-sense single stranded RNA virus from the Orthomyxoviridae family. Most human infections are due to the Influenza A or B subtype. Viral transmission is propagated via aerosolised body fluid and once inoculated into the host, the virus has the predilection to infect ciliated columnar epithelial cells lining the respiratory mucosa.

Majority of infected patients undergo an uncomplicated course of the disease while a small minority develop complications. Influenza associated complications usually involve high-risk populations including pregnant women, extremes of age, immunosuppressed patients, and patients with chronic co-morbidities. Respiratory complications preferentially involve the upper respiratory tract in children and generally involves the lower respiratory tract in adults. Pneumonia is the commonest respiratory influenza-associated complication which may be primary viral pneumonia or pneumonia from secondary bacterial co-infection. The presentation varies in severity from mild pneumonia not requiring oxygen support to ventilatory failure, acute respiratory distress (ARDS) and even death from septicaemia with multi-organ failure.

Case presentation

An 87-year-old woman with a background of hypertension, gout, dyslipidaemia and chronic kidney disease (stage 3) presented with a two-day history of an abrupt onset fever with chills, anorexia, and rhinorrhoea. This was followed by a productive cough, initially worse nocturnally but progressing into persistent cough with purulent greenish sputum. Her symptoms began two days after returning from Mecca. She otherwise denied any headaches, sore throat, chest pain, dyspnoea, muscle pain or gastrointestinal symptoms. She has completed the recommended schedule of three doses of Sinovac vaccine for SARS-CoV-2 (COVID-19) as per the Ministry of Health Malaysia, and received standard meningitis vaccination (group A, C, Y, W-135) prior to her travel. She stayed in Saudi Arabia for 10 days, performing her Umrah (Islamic pilgrimage). Her accompanying relatives had respiratory symptoms, such as coughing, toward the end of their stay in Saudi Arabia but has since recovered.

Clinical examination revealed a blood pressure of 112/53 mmHg with a pulse of 96/minute, respiratory rate of 24/minute, oxygen saturation of 88 to 91 % on room air (increased to 96% on 5 litres/minute oxygen via facemask) and a temperature of 37.5°C. There were no palpable cervical lymphadenopathies or facial tenderness. Her oropharynx was not injected. Chest auscultation revealed bilateral coarse basal crackles with bilateral expiratory wheeze and normal heart sounds. Her jugular venous pressure was not elevated and there was no evidence of peripheral oedema. The rest of her clinical examination was unremarkable.

Her laboratory investigations revealed a haemoglobin concentration of 11.5 g/dL, leukocyte count 13 x10^9/L, platelets 253 x 10^9/L, sodium 136 mmol/L, potassium 3.7 mmol/L, urea 9.8 mmol/L and creatinine of 147 µmol/L (baseline creatinine: 116 µmol/L). The leukocyte differential counts revealed a neutrophilia (10.7 x 10^9/L), lymphopenia (0.8 x 10^9/L) and monocytosis (1.5 x 10^9/L) with a lymphocyte to monocyte ratio of 0.53. The rest of her biochemical test results were unremarkable except for hypoalbuminaemia (29 g/L) and a CRP of 200 mg/L.

Her chest x-ray (CXR) revealed bilateral lower zone haziness (possible ground-glass opacity) with multiple speckled nodular opacities involving the middle and lower zones (Figure-1). Her blood and sputum cultures were negative. Her nasopharyngeal swab polymerase chain reaction (PCR) tests were negative for the middle east respiratory syndrome coronavirus (MERS-CoV), COVID-19 and Influenza-B but returned positive for Influenza-A (unspecified subtype).

We yielded a diagnosis of Influenza A pneumonia, and she was commenced on oseltamivir 75mg twice daily with antibiotic cover (5-days of intravenous co-amoxiclav and 3-days of oral azithromycin). Within 72-hours, she achieved clinical improvement with abatement of fever, rhinorrhoea and purulent sputum. Her leukocyte count (6.3 x 10^9/L), urea (3.8 mmol/L) and creatinine (90 µmol/L) normalised. Her lymphopenia and monocytosis also resolved (lymphocyte count 1.65 x 10^9/L, monocyte count 0.8 x 10^9/L). However, she continued to experience an itchy dry cough, expiratory wheezing upon auscultation and had difficulty weaning off oxygen.

She was commenced on regular inhaled salbutamol 200 µg four times daily. She did not receive any systemic or nebulised steroids throughout the admission. It took a further 11-days for her to be weaned off oxygen completely. During this time, she had a repeat CXR and cultures (blood and sputum). Her blood and sputum cultures remained negative and a repeat CXR revealed medial segment consolidation of the right middle lobe associated with bilateral lower zone bronchial and bronchiolar wall thickening and few basal nodules (Figure-2). In view of these findings, her oseltamivir course was extended to complete a 7-day course and she was given a 5-day course of Tazocin 4.5g three times daily to cover for possible secondary hospital acquired bacterial pneumonia.

Despite the above measures, her recovery remained slow but steady. Her wheezing eventually resolved and coughing improved prior to discharge. She was weaned-off oxygen completely on day-15 of her admission and maintained an oxygen saturation of 95% on room air for over 24 hours. A CXR taken at this point revealed no significant changes to the previous appearance but noted additional fine reticulations in the lung peripheries and lower zones, suggestive of interstitial pneumonitis or early fibrotic changes.

In view of her sustained clinical improvement, she was discharged with salbutamol inhalers to be taken as required and was planned for an out-patient high-resolution CT scan to assess for post-infectious parenchymal lung disease.

Discussion

We describe a case of influenza A pneumonia contracted while performing umrah. Respiratory tract infection is commonly observed following return from mass gatherings. A systematic review of respiratory tract infections among Haj pilgrims from 1980 to 2015 identified rhinovirus as the commonest viral isolate (prevalence: 5.9 – 48.8 %) followed by influenza (prevalence: 4.5 – 13.9%, mainly influenza A) and coronaviruses (prevalence: 2.7 – 13.2 %; only coronavirus 229E and OC43 detected) [1]. Since the MERS-CoV outbreak in 2012 and recent COVID-19 pandemic, all returning pilgrims from Saudi Arabia with fever and respiratory symptoms are isolated and screened for MERS-CoV, COVID-19 and Influenza in all Malaysian hospitals.

Influenza pneumonia often present with an abrupt onset of high-grade fever followed by coughing with a relatively short illness duration. This clinical feature is also highly predictive in the elderly population [2]. Our patient had an atypical presentation where she mounted a low-grade fever, and her incubation period was lengthened compared to her accompanying family members. Possible explanations may include a lower volume of viral inoculum, presence of preceding mucosal immunity and use of paracetamol.

Her clinical presentation is unique as she did not experience dyspnoea despite being hypoxic (happy hypoxaemia) and demonstrated prominent bronchospasms secondary to influenza-associated bronchitis. Happy hypoxaemia is a recognised phenomenon in COVID-19-associated pneumonia but may also occur in other respiratory pathology. The mechanism for this phenomenon is complex, involving an interplay between autonomic sensory pathways and the medullary respiratory centre.

Bronchitis causes airflow limitations accounting for wheezing and bronchial nerve irritation

leading to troublesome coughing. Histological studies indicate that respiratory epithelial cells infected with the influenza virus subsequently undergo necrosis and slough off their basement membrane [3]. This will expose underlying sensory vagal afferents which upon stimulation by surrounding inflammation, triggers coughing. These nerves (mainly unmyelinated C-fibres) are sensitive to various stimuli, therefore may persist after resolution of airway inflammation [4].

Hypoxia in our patient was reversed with supplemental oxygen, indicating a ventilation to perfusion (V/Q) mismatch. The V/Q mismatch is secondary to a combination of persistent pulmonary arterial blood flow to consolidating parts of the lung (pneumonia) and airflow limitation to the alveoli (bronchitis).

Although laboratory PCR testing did not provide subtype specification in our patient, the presence of alveolar ventilation impairment suggest infection with an avian influenza A. The influenza A virus binds to surface sialic acid receptors on respiratory epithelial cells before being internalised into the cytoplasm and subsequently nucleus, for replication. Alveolar cells express surface sialic acid exclusively containing α2,3-glycosidic bonds. It is known that human influenza A viruses preferentially binds to glycans with α2,6-glycosidic bonds (mainly distributed in the upper respiratory tract and is absent in alveolar cells) and avian Influenza A viruses exhibits predilection to glycans with α2,3-glycosidic bonds (distributed throughout the respiratory tract) [5]. Hence, avian Influenza A infection has been associated with a higher incidence of pneumonia. The main avian subtype of Influenza A adapted to humans currently are the H1N1, H2N2 and H3N2 subtypes [5].

Radiographic characteristics

The characteristic CXR appearance in influenza pneumonia is a bilateral reticulonodular shadowing associated with areas of focal consolidation with a propensity to affect the lower lobes [6]. A retrospective middle eastern study (Egypt and Saudi Arabia) analysed radiographic changes associated with influenza pneumonia during the H1N1 influenza A epidemic in 2009. Pulmonary consolidation (alveolar and confluent) was the commonest pattern seen (87.2%) followed by ground-glass opacity (72.3%) and reticulo-nodular opacities (70.2%) [7].

The diagnosis of influenza pneumonia shouldn't be based on radiographic appearance alone as there are overlapping appearance with bacterial pneumonia and certain interstitial lung diseases (such as cryptogenic organising pneumonia). Viral pneumonia generally presents with interstitial pneumonia rather than alveolar pneumonia. Radiographic presence of a lobar pneumonia may suggest a secondary bacterial component [8] although adenoviral pneumonia may demonstrate radiologically identical features (Table 1).

Secondary bacterial infection

A study conducted by the Centers for Disease Control and Prevention (CDC) on fatal cases of hospitalised patients with H1N1 influenza in 2009 revealed that 29% of these patients had bacterial co-infection. The commonest organism isolated was *Streptococcus pneumonia* (45.5%), followed by *Staphylococcus aureus* (22.7%) and *group A- streptococcal species* (22.7%) [10]. This appears to reflect community acquired organisms and oral commensals. A larger and more recent retrospective study (cohort spanning 2017 to 2020) revealed 14.4% of hospitalised influenza patients develop secondary bacterial pneumonia [11]. This study included patients with hospital acquired pneumonia (HAP) and ventilator-associated pneumonia. The commonest organism isolated was *Acinetobacter baumannii* (32%) followed by *Pseudomonas aeruginosa* (28%), *Streptococcus pneumonia* (14.3%) and *Staphylococcus aureus* (12%) [11]. This study reflects patients in the intensive care setting as 32% of patients were isolated with carbapenem-resistant organism and 4% with extended-beta lactamase (ESBL)-producing organism. Our patient had tazocin (piperacillin/tazobactam)

which covers ESBL-producing organisms including *Pseudomonas aeruginosa*.

Therapy

The mainstay of therapy in influenza pneumonia is respiratory support and anti-viral therapy. Our patient received oseltamivir and only required low-flow supplemental oxygen with inhaled bronchodilators.

Amantadanes and neuraminidase inhibitors are well-established classes of specific anti-viral agents licensed for influenza. Amantadane-resistant influenza A strains were initially discovered in 2003 and by 2009, all influenza A strains are fully resistant to this drug [12]. Current guidelines recommend neuraminidase inhibitors for treatment and prophylaxis of influenza. Derived from clinical data, their benefit is conferred when commenced within 48 hours of symptom onset [13]. However, there is still a mortality-risk reduction among critically ill patients if instituted within 5 days of symptom onset [13].

Oseltamivir is an oral neuraminidase inhibitor with the best evidence for efficacy. With widespread global use, oseltamivir-resistant influenza strains are beginning to emerge. This resistance is usually conferred by the H275Y RNA gene mutation [14]. An epidemiological analysis studying the incidence of anti-viral resistance after the H1N1 influenza pandemic in 2009 found the pooled incidence rate for oseltamivir resistance to be 2.6% (95% confidence interval: 0.7% to 5.5%) as for 2010 [15]. Currently, there are no established guidelines to recommend optimal therapy for oseltamivir-resistant influenza pneumonia. Most centres utilise nebulised zanamivir [16]. This is based on low incidence of zanamivir-resistant influenza strains [17], the CDC statement of recommendation [18] and supportive evidence from pharmacodynamic studies [19]. For critically ill patients on mechanical ventilation or extra-corporeal membrane oxygenation, intravenous agents such as zanamivir and peramivir can be utilised. However, these agents are not widely available.

Novel antiviral agents such as favipiravir and baloxavir were developed to target influenza strains resistant to both amantadanes and neuraminidase inhibitors. Favipiravir completed two multi-centric randomised controlled trials (RCT) in 2015 (US316 and US317 trials). Favipiravir significantly reduced the median time to achieve undetectable virus in nasopharyngeal swabs by 23.2 hours and 24 hours compared to placebo in the US316 and US317 trials respectively (both achieving $p < 0.001$). However, there is no significant difference in the median time to illness alleviation and return to normal activity [20]. Favipiravir is teratogenic and is currently only approved in Japan for treatment of uncomplicated influenza [20]. Baloxavir has also completed two multi-centric RCT (CAPSTONE-1 and CAPSTONE-2 trials). Both trials demonstrated statistically significant reduced median time to symptom alleviation compared to placebo by 26.5 and 25.8 hours respectively (both achieving $p < 0.001$) [21][22]. Baloxavir is not considered teratogenic and has been well tolerated in these trials. It is currently approved in Europe and other countries for treatment of uncomplicated influenza infection.

Adjuvant systemic corticosteroid therapy has been utilised in severe viral respiratory infections in attempt to limit immune-mediated lung damage and improve gas diffusion capacity. However, the clinical outcome of this strategy is variable. In acute trachea-laryngo-bronchitis (croup) and COVID-19 associated pneumonia, systemic steroid therapy has been shown to improve clinical outcomes. A meta-analysis investigating influenza associated pneumonia and ARDS found corticosteroid therapy to be associated with a higher incidence of nosocomial infection and an increased mortality (OR 1.53, 95% CI [1.16, 2.01]) [23]. A scrutiny of this analysis revealed that increased mortality affected mainly patients receiving high-dose corticosteroids (over 150mg methylprednisolone daily or equivalent) [24] or patients commenced on early

corticosteroid therapy (within 3 days of mechanical ventilation) [25]. Despite the evidence outlined above, we feel that inhaled or nebulised corticosteroids such as budesonide may be beneficial in selected patients such as our case (presented with a prominent element of bronchitis). Although no large studies have been undertaken to investigate this treatment modality, the benefit can be deduced from standard treatment for patients with acute exacerbation of obstructive airway diseases. An inhaled administration would minimise systemic adverse effects and the immune suppression expected from systemic corticosteroids.

Vaccination

The benefit of vaccination in influenza prophylaxis has been long established. Currently, two types of approved vaccines are available (inactivated virus and live attenuated virus vaccine). All modern influenza vaccines aim to stimulate production of neutralising antibodies against viral haemagglutinin antigen, which confers immune protection. Both vaccine types are effective. The inactivated influenza vaccine is widely available in Malaysia. A recent systematic review demonstrated that influenza vaccination significantly reduced the risk of laboratory confirmed influenza in elderly patients over 61-year-old (average risk ratio of 0.3) and reduces hospitalisation from influenza in all adult patients with a risk ratio ranging from 0 to 0.29 compared to placebo [26]. With the high incidence of influenza particularly during mass gatherings, it would be intuitive to offer influenza vaccination as part of the travel package for pilgrimage (Umrah, Hajj) travellers. Currently, the meningococcal ACYW-135 vaccination has been made mandatory by the Kingdom of Saudi Arabia for pilgrimage travellers. Additionally, the Ministry of Health Malaysia encourages the pneumococcal and influenza vaccination prior to travel but currently it is not mandatory.

Conclusion

Pneumonia is the commonest respiratory influenza-associated complication. The clinical presentation varies in severity and may involve different areas of the respiratory tract, depending on the influenza viral subtype. Bacterial co-infection may further complicate influenza pneumonia, conferring poorer outcomes. There is overlap between the radiological appearance of primary influenza pneumonia and secondary bacterial pneumonia, hence it is prudent to cover critically ill patients with both anti-viral and broad-spectrum anti-bacterial agents whilst awaiting specimen virological/microbiological confirmation. Specific anti-viral therapy for influenza pneumonia is currently limited to neuraminidase inhibitors. However, novel anti-viral agents have been developed and is awaiting clinical appraisal for potential utilisation in neuraminidase inhibitor-resistant influenza. Systemic corticosteroids should generally be avoided in influenza pneumonia. However, more research is needed to assess the role of inhaled/nebulised corticosteroids in selected patients. Influenza vaccination should be offered to high-risk patients to reduce the risk of developing influenza and ameliorate the severity of influenza-associated complications.

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Conflict of interest

None to declare.

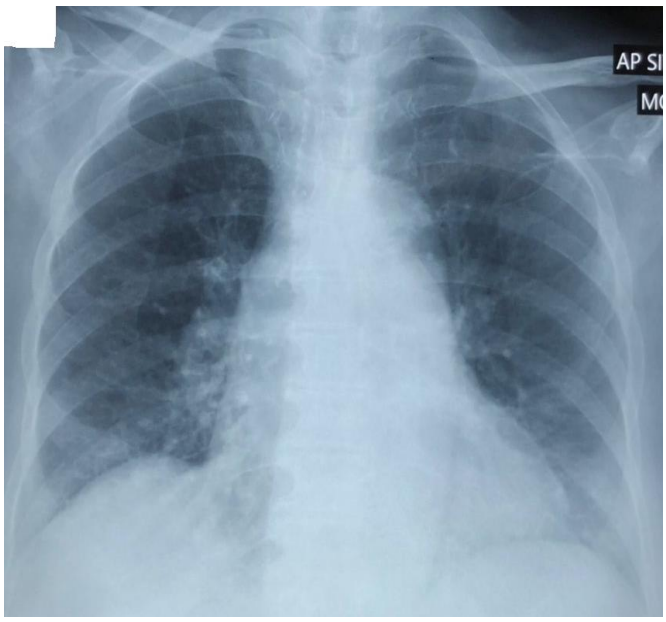

Figure 1. First chest radiograph taken at day-3 of illness. Note the multiple speckled nodules affecting the middle to lower lobes, predominantly right-sided.

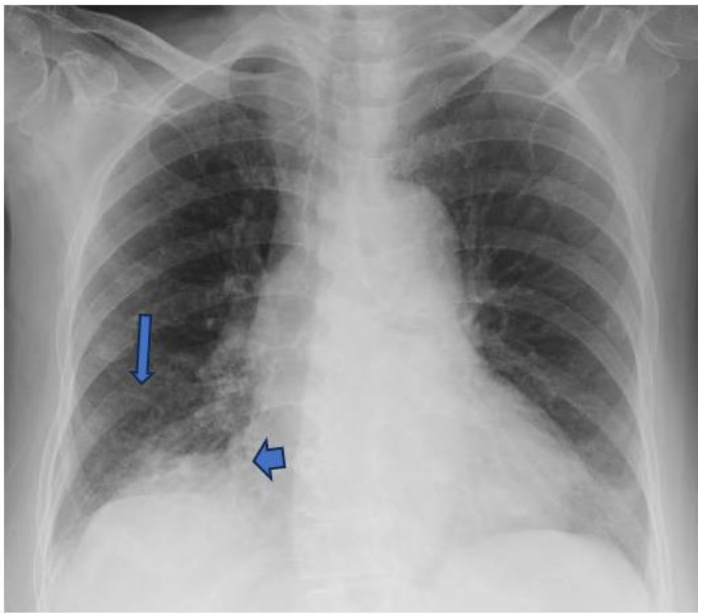

Figure 2. Second chest radiograph taken at day-16 of illness. Note the thickened bronchial walls (long-arrow) and segmental consolidation (short-arrow).

Table 1. Radiographic and clinical features of specific viral pneumonia. Adapted from Cozzi *et al* [9]. Abbreviations: GGO (ground-glass opacity), ARDS (acute respiratory distress syndrome), IVIG (intravenous immunoglobulins).

Virus	Chest x-ray appearance	Presentation	Therapy
Influenza A	Bilateral reticulo-nodular opacities with multi-focal consolidation (usually lower lobes)	Flu-symptoms followed by cough, dyspnoea and respiratory deterioration	Discussed in this article
COVID-19	Sub-pleural consolidation with bilateral GGO and reticulo-nodular opacities	Like influenza A	Dexamethasone, interleukin-6 inhibitors, Paxlovid™ (unlicensed for severe infections)
Varicella	Bilateral multi-focal nodules (representing haemorrhagic necrosis, may calcify)	Chest pain, haemoptysis and respiratory failure (1 to 6 days post rash eruption)	Aciclovir
Herpes simplex	Bilateral multi-focal GGO with segmental reticular consolidation (mainly upper lobes) ± pleural effusion	ARDS preceded by mucocutaneous disease	Aciclovir, cidofovir
Adenovirus	Bilateral multi-focal GGO with segmental/lobar consolidation	ARDS ± classical adenoviral features	Cidofovir
Cytomegalovirus	Bilateral asymmetrical GGO with multi-focal consolidation	ARDS ± preceded by infectious mononucleosis syndrome	Ganciclovir, foscarnet
Ebstein-Barr	Mediastinal lymphadenopathies ± diffuse GGO and reticular opacities	ARDS usually not preceded by infectious mononucleosis syndrome	Steroids, IVIG

Table 2. Pharmacological features of drugs used in influenza. Abbreviations: PO (oral), Inh (inhaled), Nebs (nebulised) IV (intravenous), RNA (ribonucleic acid)

Drug class	Mechanism	Drug	Route of administration	Main side effects	Special consideration
Amantadane	Inhibits influenza A-M2 ion channels, disabling release of viral RNA into host cytoplasm.	Amantadine Rimantadine	PO	Anticholinergic side-effects, elevated serum creatinine, livedo reticularis	Not active in influenza B. Currently used to treat Parkinson's dyskinesia.
Neuraminidase inhibitor	Inhibits influenza A/B neuraminidase, preventing release of virions from infected cells	Oseltamivir	PO	Nausea, vomiting, abnormal liver function test.	Most widely used agent worldwide.
		Zanamivir	Inh, Neb, IV	Bronchospasm	Caution in patients with obstructive lung diseases.
		Laninamivir	Inh (single dose)	Nausea, vomiting, diarrhoea.	Post-exposure prophylaxis only
		Peramivir	IV (single infusion)	diarrhoea	For treatment of uncomplicated influenza
Nucleoside analogue	Inhibits viral RNA-dependent RNA polymerase	Favipiravir	PO	Teratogenic, transient hyperuricaemia	In-vitro activity against many other RNA viruses
Endonuclease inhibitor	Inhibits influenza cap-dependent endonuclease	Baloxavir	PO (single dose)	nausea	Used for neuraminidase-resistant influenza strains.

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