CASE REPORT

H1N1 pneumonitis associated with long-term non-steroidal anti-inflammatory drug abuse

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SUMMARY

This case series discusses two similar presentations of H1N1 influenza in young patients with a background history of long-term non-steroidal anti-inflammatory drug (NSAID) abuse. Both patients presented with type 1 respiratory failure requiring intensive care unit admission and subsequent organ support. This report reviews the immunosuppressive effects of long-term NSAID use and highlights a potential link to the significant morbidity seen.

BACKGROUND

The H1N1 virus strain is a subtype of influenza A, and was responsible for the 2009 pandemic. Although only a minority of infected patients require hospitalisation (1.3–2.5% in the UK¹), those who do frequently require treatment in intensive care unit (ICU) (10–30%¹). The majority of ICU admissions present with a diffuse viral pneumonia, often leading to rapidly progressive respiratory failure and acute respiratory distress syndrome (ARDS).¹

The literature from the 2009 H1N1 pandemic indicates risk factors for development of severe H1N1 include immunosuppression, obesity, pregnancy and underlying respiratory disease.^{2–3} The two cases discussed below illustrate a further, and perhaps under-reported risk factor, for the development of severe sequelae of H1N1 influenza.

Non-steroidal anti-inflammatory drug (NSAIDs) are commonly used therapeutically as anti-inflammatory and antipyretic agents. However, they are also known to have immunosuppressive properties and are a risk factor for development of the systemic inflammatory response syndrome in viral infections.^{4–5} These cases highlight two examples where NSAID abuse may have been a significant factor in the development of severe pneumonitis secondary to H1N1 influenza.

CASE PRESENTATION**Case 1**

A 45-year-old man presented to the emergency department with shortness of breath, on a background of 3 days of flu-like symptoms. Medical history included hepatitis C due to intravenous drug use 20 years earlier, and recent recurrent urinary tract infections under investigation by urologists. The patient was a smoker (20 pack year history) and admitted addiction to codeine; he had been taking 4.8 g ibuprofen and 307 mg codeine per day, in the form of over the counter 'Nurofen plus' tablets, for the past 5 years.

On examination, the patient was in respiratory distress, and looked thin and pale. Auscultation of his chest revealed bilateral crackles throughout both lungs. His pO₂ was 14 kPa on 15 L oxygen via Hudson mask with reservoir bag, and pCO₂ was 3.4 kPa. He was haemodynamically stable and notably had a profound metabolic acidosis (pH 7.19, base excess –19 mmol/L, HCO₃ 6.8 mmol/L).

Blood results showed C reactive protein (CRP) 310 mg/L, normal white cell count (WCC) and an acute kidney injury (creatinine: 191 µmol/L, baseline 100 µmol/L). Chest X-ray showed bilateral interstitial shadowing spreading from both heart borders but no focal consolidation.

The patient was admitted to ICU for respiratory support with non-invasive ventilation and for correction of his metabolic acidosis, thought to be a renal tubular acidosis secondary to NSAID use. His respiratory function deteriorated significantly over the following 48 h, requiring tracheal intubation and mechanical ventilation. His repeat chest X-rays showed worsening diffuse interstitial infiltrates, and his clinical picture was consistent with severe ARDS, with a PAO₂/FiO₂ ratio of 90.

He was started on oseltamivir empirically, in addition to piperacillin/tazobactam and clarithromycin, to cover for severe community-acquired pneumonia and atypical pathogens. His H1N1 swab results were positive and he was also found to be pneumococcal antigen positive. He remained persistently feverish. Ten days into his admission, bronchoscopy and alveolar lavage showed frank pus and he was subsequently treated for a likely ventilator acquired pneumonia. Sputum samples grew pseudomonas, acinetobacter and non-albicans candida, and he was escalated to meropenem and started on fluconazole to cover fungal infection. He required inotropic support while ventilated and sedated, and though his renal function was impaired, he never required haemofiltration. He had a tracheostomy inserted on day 15 of admission.

CT of the chest after 17 days (figure 1) showed extensive consolidation and ground glass change throughout both lungs, consistent with widespread severe pneumonitis. His case was discussed with the respiratory team locally and with a tertiary referral centre due to inability to wean his ventilatory support. On day 30 of admission he was given pulsed methylprednisolone with a dramatic improvement in ventilation after 48 h.

Case 2

A 40-year-old woman presented to the emergency department with shortness of breath for 3 days on

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Figure 1 Case 1 chest CT.

a background of 2 weeks of flu-like symptoms. She had been seen by her general practitioner and at another accident and emergency department in the previous week and discharged with oral amoxicillin. Medical history was of longstanding anaemia (previously investigated with no cause found), occasional migraines, depression and controlled epilepsy. Social history revealed addiction to 'Nurofen plus' and zopiclone; she had been consuming approximately 4 g ibuprofen with 250 mg codeine per day recently, with 15 mg zopiclone at night. She also took mirtazapine, duloxetine, carbamazepine and ferrous fumarate daily on prescription.

On examination, she was in respiratory distress, lethargic and looked thin and pale. Auscultation of her chest revealed bilateral fine crepitations throughout both lung fields. She was in type 1 respiratory failure with a pO_2 of 9.4 kPa and pCO_2 of 4.3 kPa on 15 L oxygen via Hudson mask with reservoir bag. She was haemodynamically stable but had a compensated metabolic acidosis with a pH 7.37, BE of -5 mmol/L and HCO_3^- of 20 mmol/L. Her blood tests showed CRP 290 mg/L with WCC $11 \times 10^9/L$ and were otherwise unremarkable. Chest X-ray (CXR) showed bilateral interstitial infiltrates.

The patient was treated empirically with oseltamivir for presumed viral pneumonitis, and piperacillin/tazobactam and

clarithromycin for community-acquired pneumonia. Viral PCR for H1N1 antigen was later confirmed positive. She was started on intravenous fluids for presumed NSAID-related metabolic acidosis. She was transferred to ICU and received non-invasive ventilation, which improved her oxygenation. She remained stable over the following 48 h, but deteriorated slightly on day 4 of admission, with new pleuritic chest pain and right mid-zone consolidation on CXR. Antibiotics were escalated to meropenem to cover hospital acquired pneumonia. She also reported right calf swelling, rather than CT pulmonary angiogram on day 7 (figure 2) of admission showed diffuse pneumonitis with bilateral pleural effusions but no evidence of PE. By day 10 of admission, her respiratory function had improved significantly and she was adequately saturating on facemask oxygen alone.

OUTCOME AND FOLLOW-UP

Case 1: At the time of writing, the patient is receiving minimal ventilatory support through a tracheostomy tube, but his recovery has been complicated by development of spontaneous bilateral persistent pneumothoraces. Other organ function has recovered fully. He has been referred to a cardiothoracic unit for further management.

Case 2: The patient has made a full recovery and has been discharged home.

DISCUSSION

A literature search did not reveal other similar case reports of severe H1N1 pneumonitis associated with long-term NSAID abuse. However, a letter published in *The BMJ* in 2009⁶ (with reference to the H1N1 pandemic), postulated NSAID use may aggravate the symptoms of influenza infection and potentially predispose to the development of multiorgan failure. Two examples are used: first, the incidence of Reye's syndrome in children has significantly fallen since the discontinuation of aspirin among the paediatric population; second, in Japan, the incidence of fatality from influenza associated encephalopathy has significantly reduced since use of diclofenac and mefenamic acid were restricted in 2000.

Cianferoni *et al*⁵ found that anti-inflammatory salicylates can influence the nature of the adaptive immune response by selectively inhibiting the expression of IL-4 in CD4 T-cells. Inaoka *et al*⁴ went on to examine whether NSAIDs could selectively inhibit cytokine production by innate immune cells; they found that early IFN- γ production by innate immune cells, the most efficient strategy for antiviral defence, was impaired by NSAIDs. They concluded that it was possible that the frequent use of NSAIDs during viral infections may cause an overexuberant acquired immune response to the virus to compensate for the decreased antiviral innate immune responses.

In an article published in 2012, Truter discusses the previous debate around the use of NSAIDs during the 2009 influenza outbreak. She notes the similarity in findings from the 1918 and 2009 influenza pandemics; that the use of aspirin or NSAIDs, respectively, may be an important contributory cause for deterioration. More specifically, she comments on the progression to acute lung injury and multiorgan failure induced by hypercytokinaemia, the induction of which is promoted by NSAIDs, and which has been shown to increase the mortality of infected animals. She goes on to suggest that NSAID use may have been a factor in many deaths associated with the H1N1 influenza and that further research exploring the action of NSAIDs on respiratory inflammation is required to substantiate such claims.⁷

On a different point, in the cases discussed, one patient was given pulsed methylprednisolone on day 30 due to on-going

Figure 2 Case 2 CT pulmonary angiogram.

pneumonitis and pulmonary infiltrates on his chest CT. While steroid therapy is often used in patients with ARDS secondary to viral pneumonia, on review of the literature, its role is not established. Brun-Buisson *et al*⁸ found no beneficial effect of corticosteroids in this group of patients but found that very early corticosteroid therapy may be harmful. A 2011 observational study by Martin-Loeches *et al*⁹ concluded that early use of corticosteroids in patients affected by H1N1 influenza infection did not result in better outcomes and was associated with increased risk of superinfections.

In conclusion, both the cases discussed in this report support the hypothesis that NSAID use may cause suppression of the innate immune response to viral infections. This may have been a factor contributing to the severe respiratory failure seen in these individuals. As NSAIDs remain an active ingredient in

many over-the-counter influenza preparations, this highlights an important area for further research.

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Contributors EP collected the information on the patients, and obtained their consent. She researched the topic, found relevant supporting information, and wrote the case report and the full article. OH helped with formatting, submission and revision of the article. CO helped HER to decide on target journal and audience and made suggestions, corrections and some minor additions.

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Learning points

- ▶ Non-steroidal anti-inflammatory drug (NSAIDs), while commonly used as antipyretics and anti-inflammatories in the community, may have immunosuppressive effects.
- ▶ These cases support the possibility that NSAID use, and particularly NSAID abuse, could be considered a risk factor for complications and increased severity of disease associated with H1N1 influenza.
- ▶ This report points to the need to carry out epidemiological studies to determine if there is an association between long-term NSAID abuse and adverse outcome of influenza.

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