Co-infection of influenza A with Staphylococcus aureus causing bacterial arthritis in a child

Yahya Amar Mari, Syed Ahmed Zaki, Ahmed Bashir Yagan

Influenza viruses are responsible for an average of 500,000 deaths per year globally. Various factors, including bacterial co-infection, increase the severity of influenza infection as observed during previous influenza pandemics and seasonal epidemics. Several cases of bacterial co-infection with influenza resulting in severe pneumonia and sepsis have been reported. However, co-infection leading to bacterial arthritis without overt pulmonary involvement has not been reported till date. We herein report this rare case of a six-year-old previously healthy boy with influenza A, who developed bacterial arthritis after co-infection with Staphylococcus aureus (S. aureus) and was managed successfully.

Case report

A six-year-old Arab boy presented with bilateral lower limbs pain, inability to walk and bear weight on legs. He had fever, cough and runny nose for three days prior to his presentation. Fever was high grade, intermittent and responded transiently to antipyretics. There was no headache, vomiting, diarrhoea, recent intramuscular injection or any history of trauma. There was no history of past or current skin disease. His past and developmental history were normal. His routine childhood immunizations were up-to-date, however he had never received influenza vaccine. On examination he was conscious, alert with temperature of 39.2 celsius, heart rate of 122/min, respiratory rate of 24/min and blood pressure of 104/64mmHg. There was nasopharyngeal congestion. The child was unable to walk but could stand with support. Tone was normal in all four limbs with normal superficial and deep reflexes. There was marked bilateral calf tenderness. His spine and cranial nerve examination were normal. Rest of the systemic examination was normal. He was admitted with a provisional diagnosis of viral myositis. His serum creatine phosphokinase was 4,000U/L (normal 39–308U/L) and nasopharyngeal swab was positive for influenza A virus. Complete blood count and C-reactive protein (CRP) were normal. Tests for other viruses were negative. He was started on intravenous fluids and paracetamol PRN. We considered persistent fever and inability to walk and stand in our patient as probably due to severe/progressive influenza and hence started oseltamivir. Calf pain improved over the next two days with gradual improvement in the mobility. On third day of admission, the child still had low-grade fever and the next day developed severe pain in the left hip and thigh with inability to walk. Repeat septic workup showed increased inflammatory markers. The total leucocyte count was 18,300/cumm, CRP was 303.9mg/L (normal- <9) and erythrocyte sedimentation rate was 104mm/first hour. His alanine transaminase was 230U/L [N 0–63] and aspartate transaminase was 528U/L [N 15–37]. Hence intravenous amoxicillin-clavulanate was started empirically. Ibuprofen was started round the clock for the pain and inflammation. Ultrasound of the left hip showed synovial thickening of left hip joint with effusion. Arthroscopy was done and the joint was drained. The synovial fluid culture and the blood culture grew S. aureus and intravenous flucloxacillin was started as per the sensitivity pattern for the treatment of septic arthritis. Nasopharyngeal swab culture grew S. aureus. The S. aureus isolated from the blood culture, synovial fluid and the nasopharyngeal swab had the same antibiogram. Flucloxacillin was given intravenously for 21 days followed by oral for seven days after discharge. Physiotherapy was started after...
the pain subsided and gradual improvement noted in movement of the left lower limb. Magnetic resonance imaging showed features consistent with bacterial arthritis with enhancing foci in the acetabulum and proximal femur suggestive of osteomyelitis (Figure 1).

Repeat inflammatory markers, liver function tests and blood cultures were negative at the end of the treatment. The power and function of the lower limbs were normal and there were no sequelae on follow-up after six months.

Discussion

Early diagnosis and prompt antibiotic treatment were crucial in the complete recovery of the child. In contrast to other published studies, our case was unique as the co-infection lead to bacterial arthritis without acute lung injury. Bacterial co-infection complicates approximately 0.5% of all influenza cases in previously healthy individuals. This increases to at least 2.5% in people with predisposing conditions like extremes of age (>65 years or <5 years) and those with pre-existing chronic medical conditions or immunosuppressive conditions. Pathogens that colonise the nasopharynx, including \textit{S. aureus}, \textit{S. pneumoniae}, and \textit{S. pyogenes}, are the most commonly isolated bacteria. In the presence of influenza infection, these opportunistic pathogens can cause bacteremia and severe infection. In a systematic review and meta-analysis of 27 studies done by Klien et al on the frequency of influenza and bacterial co-infection, \textit{S. pneumoniae} (35%) and \textit{S. aureus} (28%) were the most common co-infecting bacteria. The nasopharyngeal swab culture, synovial fluid and blood culture of our patient grew \textit{S. aureus} with the same antibiogram. Williams et al in their study found that children with influenza having bacterial co-infection had an increased likelihood of requiring intensive care unit admission, a longer

\textbf{Figure 1:} MRI of the left hip joint showing features suggestive of bacterial arthritis with enhancing areas suggestive of osteomyelitis in the acetabulum and left proximal femur and in the periarticular soft tissues. Also seen is peripheral enhancing collection in the joint extending into left gluteus medius muscle.
hospital stay and a trend towards higher mortality. This occurs due to the epithelial cell damage and increased receptor availability during influenza infection, which enables the invading bacteria to adhere and grow. Table 1 summarises the factors which lead to increased severity of illness during co-infection.

Co-infection predominantly occurs during periods of high influenza viral shedding and maximum tissue damage (ie, 3–7 days after influenza infection), but may occur concurrently with or shortly after influenza infection. Non-steroidal anti-inflammatory drugs [NSAID] like ibuprofen, aspirin have strong anti-inflammatory effects. They can modify the signs and symptoms leading to delayed diagnosis and management. Factor et al also found NSAID as a risk factor for invasive Group A Streptococcal infection.

We had managed our patient initially with paracetamol PRN, which has mild anti-inflammatory action. Hence the possibility of NSAID modifying the course of the disease doesn’t arise in our case.

The management of bacterial co-infection includes prevention, early diagnosis and appropriate treatment of both influenza and bacterial infection. However, clinically, it can be sometimes difficult to identify bacterial co-infection, given the substantial symptom overlap of influenza and bacterial infections. As per the updated 2018 clinical practice guidelines by the infectious disease society of America (IDSA), clinicians should investigate and empirically treat bacterial co-infection in patients with suspected or laboratory-confirmed influenza who present initially with severe disease (extensive pneumonia, respiratory failure, hypotension, sepsis and fever). Bacterial co-infection should also be considered in patients who deteriorate after initial improvement on antivirals and/or fail to improve after 3–5 days of antiviral treatment. In a study done by Zhihao et al, significantly higher procalcitonin and CRP levels were detected in the bacterial co-infection group than in the influenza infection-alone group. Thus the combination of these markers could assist in identifying bacterial co-infection during the early disease phase, although clinical judgement is also indicated. As per IDSA, the empiric antibiotic treatment for any suspected bacterial co-infection in influenza patients should cover the most common isolated bacteria, ie, S. aureus, S. pyogenes and S. pneumoniae. Coverage for additional pathogens may be necessary based upon the child’s age, particular clinical circumstances, site of infection, gram stain and the local antibiotic resistance pattern.

Table 1: Factors contributing to the increased severity of influenza illness during bacterial co-infection.

<table>
<thead>
<tr>
<th>Viral factors</th>
<th>PB1-F2 – increases susceptibility to bacterial infection</th>
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<tr>
<td>Bacterial factors</td>
<td>Staphylococcus aureus: produces proteases which cleave hemagglutinin, thus producing fusion-competent virus particles with enhanced infectivity</td>
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<td>Mechanical factors (host)</td>
<td>Epithelial injury</td>
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<td></td>
<td>Impaired mucociliary velocity</td>
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<td>Immune cells (host)</td>
<td>Impaired neutrophil function and recruitment</td>
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<td></td>
<td>Increased neutrophil apoptosis</td>
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<td></td>
<td>Macrophages and monocytes—reduced phagocytic capacity</td>
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<tr>
<td>Cytokines/chemokines (host)</td>
<td>IFN-γ &amp; IFN-α/β</td>
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<td></td>
<td>1. Decrease the production CCL2, which is required for macrophage recruitment</td>
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<td></td>
<td>Keratinocyte derived chemokine [KC] &amp; Macrophage inflammatory protein 2 [MIP-2]</td>
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<td></td>
<td>– Downregulation of KC and MIP-2 leading to inhibition of migration of neutrophils.</td>
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<tr>
<td>Pattern recognition receptors (host)</td>
<td>MARCO [macrophage receptor with collagenous structure]—downregulation of MARCO leading to reduced phagocytic activity of macrophages and monocytes.</td>
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Cultures should be taken before starting antibiotics empirically in influenza cases with suspected bacterial co-infection. The antimicrobial regimen can later be de-escalated as necessary or tailored to a specific pathogen based on microbiological results. This will avoid patient exposure to the risks of prolonged unnecessary antibiotic use.

Human data are limited regarding the effectiveness of oseltamivir treatment in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Thus the best way currently to prevent serious co-infections is to prevent the antecedent viral infection entirely. Studies have shown up to a 45% reduction in pneumonia hospitalisations and mortality rates following influenza vaccination. Thus annual influenza immunisation for >6 months of age remains an important tool for prevention of severe influenza illness commonly associated with bacterial co-infection. Influenza vaccination can have substantial epidemiological impact even when vaccine efficacy is low. As per Sah et al, the mortality and overall health burden due to influenza infection is more sensitive to changes to vaccination coverage than to changes in vaccine efficacy. Thus reduced motivation to vaccinate could present a greater danger than low vaccine efficacy itself.

Conclusion
Influenza and bacterial co-infections can cause severe illness with increased morbidity and mortality. Physicians should maintain increased vigilance in influenza for early detection and investigation for risk of serious secondary bacterial infection. Annual influenza vaccination for >6 months remains the best way to prevent infection and reduce seriousness of illness even if one gets infected.

Competing interests:
Nil.

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