Severe Pneumonitis in Omani Infants During An In-Hospital Measles Outbreak

A report of three cases

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Abstract
Measles is a highly contagious infectious disease. Despite aggressive national initiatives to eradicate measles, outbreaks have occurred in recent years. We report three infants with measles who developed pneumonitis, received intensive care treatment and made full recoveries. Infants can have an atypical presentation and develop severe symptoms. Pneumonitis is a serious complication, and the management strategies are controversial. The early detection of measles and isolation of affected individuals play major roles in the elimination of measles outbreaks.

Keywords: Measles, Pneumonitis, Infant, Complication, Respiratory Distress Syndrome, Vitamin.

Introduction
Measles is a highly contagious and potentially fatal viral illness that is especially dangerous for infants and malnourished and immunocompromised patients who can develop atypical and severe manifestations. 1 The causative pathogen belongs to the Paramyxoviridae family and is mainly transmitted by respiratory droplets. Measles can be prevented by the available vaccine. 2
The symptoms of measles are often mild; however, infants and malnourished and immunocompromised patients can develop atypical or severe manifestations, including pneumonia, acute disseminated encephalomyelitis, and subacute sclerosing encephalitis.³ Measles-associated mortality declined following the implementation of vaccination programs, though outbreaks of cases continue to occur when unvaccinated individuals are exposed to the virus.² The incidence of measles incidences in Oman is low (0.53 per 100 000 person-years), and the measles vaccine coverage has been consistently above 95% since 1990.⁴ In Oman, the measles vaccine is administered to all children at 12 and 18 months of age, as recommended by the WHO. However, the CDC and WHO guidelines recommend the administration of the measles vaccine at 9 months of age during measles outbreaks.⁵

Gulf countries have implemented a vaccination schedule involving 2 doses of the MMR vaccine, with the first dose at 12 months of age. The measles vaccine coverage in Bahrain has been more than 90% since 1993 and has been sustained at >97% since 2001.⁶ Vitamin A supplementation is recommended by the WHO for all children with measles.⁷

Measles-related pneumonia is a life-threatening complication that can lead to severe acute lung injury and acute respiratory distress syndrome. Co-infection with other viruses and bacteria is not uncommon. The treatment for measles-related pneumonia primarily involves supportive care. In this article, we report three infants who developed measles-related pneumonia following exposure of the second and third patients to the index case during a hospitalization. The early detection of measles, isolation of the affected individuals, and performance of sensitive investigations in all contacts are needed to prevent the transmission of measles.

Case One
A previously healthy six-month-old male infant was admitted to the Royal Hospital in December 2019 with febrile illness and a generalized rash of four days duration. On examination, he was lethargic, dehydrated, febrile and had a normal respiratory rate with bilateral normal breath sounds. He had a maculopapular rash on the face, trunk and over extremities. He was admitted in the general ward initially suspecting acute viral fever for hydration with intravenous (IV) fluids. On day three of admission, he became tachypnoeic, tachycardic, febrile with oxygen saturation
of 88-90% in room air, so he was transferred to high dependency unit (HD) for close monitoring and oxygen support via facial mask suspecting acute bronchiolitis.

The patient’s complete blood count (CBC) test showed normal white blood cell 4.0 x 10^9/L (normal range: 1.4–9.0 x 10^9/L) with normal neutrophils and lymphocyte count. He received dexamethasone, adrenaline nebulization and oseltamivir. A nasopharyngeal viral multiplex polymerase chain reaction (PCR) test was reported negative for respiratory viruses including RSV, influenza A and B, rhinoviruses, parainfluenza, coronavirus, adenoviruses, bocavirus, enteroviruses, paraechoviruses, human metapneumovirus and *Mycoplasma pneumonia*.

His hospital stay was complicated with the development of respiratory distress and clinical sepsis requiring admission to the paediatric intensive care unit (PICU) on day three and the use of non-invasive ventilation (NIV). A chest X-ray (CXR) showed bilateral lung infiltration [Figure 1]. His vital signs on admission to the PICU showed persistent tachycardia (170 beats/min) with fever (38°C) and tachypnoea (70 breaths/min) with saturation above 93% on NIV.

On detailed clinical assessment, he was found to have Koplik spots and bilateral conjunctivitis. A nasopharyngeal swab PCR test was reported positive for measles. Measles IgM antibody test was positive. He required NIV support, which was weaned within one day and then, he was transferred to an isolation room. He required oxygen for 3 days following that he was discharged uneventfully to home on day 8 of admission. A detailed examination of this case by infection control specialists did not reveal the source of the infection.

**Case Two**

A nine-month-old female infant was diagnosed with tracheoesophageal fistula for which she underwent an operation; previously, she had been diagnosed with hypotonia, developmental delay, and hypothyroidism. Additionally, she underwent investigations due to the suspicion of a glycogen storage disorder. She was admitted for endoscopic dilatation of the oesophageal stricture during which she was exposed to the patient described in Case One. Ten days after exposure, she developed a high-grade fever with cough and irritability. A maculopapular rash
appeared on day 2 of her illness. Physical examination revealed a generalized maculopapular rash, a pulse rate of 170 beats/min, and a blood pressure of 100/58 mmHg with tachypnoea; therefore, she was transferred to the PICU.

Her CXR showed bilateral lung opacities. Her CBC showed leukopenia 2.9 x 10^9/L, and lymphopenia 0.4 x 10^9/L (normal range: 4-10.5) with normal neutrophils. Also, her inflammatory marker levels were high, with an erythrocyte sedimentation rate (ESR) of 72 mm/hr (normal range: 0 to 20) and C-reactive protein level of 89 mg/dL (normal range: <10). She was started on NIV for respiratory distress. Her pulmonary condition worsened clinically and radiologically with characteristics of acute respiratory distress syndrome (ARDS); therefore, the mode of respiratory support was changed to invasive ventilation. She also required inotropic support with an infusion of adrenaline.

She had persistent fever despite antibacterial treatment and negative blood and tracheal cultures and was, therefore, treated for atypical Kawasaki disease in view of features of prolonged fever and rash for 10 days duration. However, a nasopharyngeal swab PCR test revealed a positive test for measles and her measles IgM test was also positive. She received 1 day of high-dose methylprednisolone. She met the criteria for a diagnosis of ARDS with a PO2 to FiO2 ratio of 122, indicating severe acute lung injury. As part of the management strategy for ARDS, she was treated with a lung-protective ventilation strategy with the airway pressure release ventilation (APRV) mode for 7 days and 80% maintenance fluids. Treatment for measles-related pneumonia included the administration of vitamin A for 48 hours and ribavirin for 5 days. Over the course of five days in the PICU, she gradually improved, and she was extubated on day seven after admission to the PICU. She was transferred to the paediatric ward, where she stayed for 3 weeks. She continued to need supplemental oxygen, although that requirement was resolved before discharge.

**Case Three**
An 11-month-old female infant diagnosed with trisomy 21 who underwent surgery for ventricular septal defects was admitted with acute bronchiolitis and needed NIV support. She was discharged home but readmitted with febrile illness, respiratory distress, and maculopapular
rash. Her history revealed exposure to the patient described in Case One during hospitalization 10 days before presentation. On examination, her temperature was 39.3°C, with a blood pressure of 102/62 mmHg, heart rate of 168 beats/minute and respiratory rate of 60 breaths/minute with oxygen saturation of 86% in room air, therefore, required NIV and PICU care. She had a generalized maculopapular rash with a wheezy chest. Investigations revealed normal CBC and negative blood culture. A CXR revealed bilateral infiltration [Figure 2], and she was, therefore, treated for suspected measles-related pneumonitis or acute viral bronchiolitis. Nasopharyngeal swab for viral multiplex PCR test was positive for measles and negative for other viruses. Measles IgM antibody test showed a positive result. She required NIV for one day in the PICU due to respiratory distress. She was started on dexamethasone, Vitamin A, ceftriaxone and oseltamivir. She had gradual improvement and showed complete recovery on the third day of admission and was transferred to the paediatric ward isolation room. She was observed in the hospital for breathing difficulty and oxygen requirement and was discharged after three weeks stay breathing room air.

**Discussion**

To our knowledge, this is the first case series from Oman to report three infants with severe respiratory manifestations related to measles. Measles is a highly contagious disease with a transmission rate of at least 90%.

4 It can be prevented by the available vaccine, adherence to infection control measures, and careful investigations of all reported measles cases.

4 Oman had measles outbreaks from 1992 to 1993 and 2016 to 2017. These outbreaks were attributed to imported cases leading to infections among the susceptible population, which is mainly composed of unvaccinated persons (unpublished data). To increase awareness, the Ministry of Health introduced many measures aimed at eliminating measles, including introducing the fever and rash surveillance program in 2004, developing national measles guidelines, and conducting training workshops. Widespread catch-up vaccine campaigns were conducted in March 1994 and 2017 that targeted the susceptible population.

4 In their meta-analysis, Nic Lochlainn et al. showed that the measles vaccine is safe and effective for children less than 9 months of age and that its early administration it is an important step to reduce severe manifestations. However, it is challenging to sustain herd immunity in Oman as not all population had received measles vaccine.
Measles-related pneumonia is serious and is associated with high mortality, especially in children less than 5 years of age and malnourished and immune-compromised children. The described lung changes in patients with measles-related pneumonia include congestion, necrosis, and exfoliation of bronchial and bronchiolar mucosa. These lung changes lead to increased susceptibility to other forms of viral and bacterial pneumonia, thus increasing the risk of acute lung injury and ARDS.

Approximately 10%-11% of all measles-related admissions require intensive care support for respiratory support. Coetzee et al. reported that the rate of mortality due to severe measles was higher than the rate of mortality due to other causes among a cohort of paediatric intensive care patients (the measles-related mortality rate was 31%, and the non-measles-related mortality rate was 8.8%). The most common cause of measles-related mortality is ARDS with progressive respiratory failure (56%).

The majority of those admitted with severe pneumonia required ventilator support. ARDS and the presence of air leaks such as pneumothorax are associated with worse outcomes. The therapeutic strategies for ARDS include the initiation of lung-protective mechanical ventilation, lung recruitment manoeuvres, fluid management, and the appropriate application of muscle relaxants. Our second patient was treated using lung-protective strategies, lung recruitment, and fluid restriction in addition to supplementation with vitamin A and ribavirin. None of these patients had received the measles vaccine before the as all of them are less than 1 year of age and the immunization policy of the country is to vaccinate between 12 to 18 months of age.

Two of these patients had underlying chronic complex medical problems. The first patient was admitted with a history of fever, rash and conjunctivitis without a history of positive contact with a suspected or confirmed case. As the incidence of measles is low in Oman, measles was not suspected in our first patient; therefore, he was admitted to the general ward rather than being isolated. The second and third patients were exposed to the first patient. Therefore, this study emphasizes the need to increase awareness of and adherence to infection control measures to prevent an in-hospital outbreak. All of the reported patients had to be transferred to the PICU.
transfer due to hypoxemia and the need for respiratory support. One patient developed ARDS, but none of our patients had air leak syndrome. The child with ARDS required invasive mechanical ventilation, while the other two had milder forms of respiratory distress and needed NIV support. All patients were treated supportively with vitamin A and appropriate antibiotics, as CXR showed pulmonary infiltration. The second patient was initially suspected to have atypical Kawasaki disease based on her history of a prolonged fever lasting 10 days, high levels of inflammatory markers, and suspected coronary dilation on echocardiography. However, upon reviewing the echocardiography findings, coronary dilatation was ruled out. She showed clinical and radiological improvement one day after starting high-dose IV immunoglobulin (IVIG) and methylprednisolone. However, her improvement could also be attributed to the change in ventilation and fluid restriction.

Despite recent advancements in medicine, the management of measles still relies primarily on supportive care and includes hydration, the administration of antibiotics for secondary bacterial infections, and supplementation with vitamin A. A few studies have shown that the use of IV methylprednisolone is associated with improved patient outcomes. However, there have been no randomized controlled trials supporting the use of high-dose methylprednisolone in the treatment of measles-related pneumonia. Meduri et al. demonstrated that early use of a low dose of methylprednisolone in patients with ARDS resulted in an improvement in oxygenation and reduction in duration of mechanical ventilation and ICU length of stay.

Infection with measles can lower the immune function. IVIG has been used successfully for measles post-exposure prophylaxis, however, it’s effectiveness in the treatment of measles pneumonia has not yet been identified. IVIG may be used for measles pneumonia to boost the body's immune function, inhibit inflammatory reactions and thereby, accelerates the improvement of symptoms.

In total, 10 patients were admitted with a diagnosis of measles to Royal Hospital, Oman, over the 7 years from 2013 to 2019. Three of them needed ICU admission (the cases reported in this study), four were discharged from the emergency room, and the remaining 3 were admitted to
the paediatric ward for fluid support. The average hospital stay was 2 to 3 days for those admitted to the general ward.

None of the 10 patients had received the measles vaccine, and nine of them were younger than 1 year old. There was a history of positive contact with a suspected or confirmed case for 8 patients. The diagnosis of measles was made based on the finding of relevant clinical symptoms, and the diagnosis was confirmed by positive serological tests, PCR from throat swab samples, and the isolation of the virus from urine samples. This study was approved by the Royal Hospital Scientific Research Committee (SRC#CR26/2020). The authors thought the consent was not required as it doesn’t contain personal data or intervention.

**Conclusion**

Health care providers need to increase their awareness of the criteria for the diagnosis of the measles, especially in countries where the incidence of measles is low. Measles should be suspected in all unvaccinated infants and children presenting with fever and rash, and diagnostic assessments should include surveillance for the pathognomonic signs of measles. Adhering to the required infection control measures is essential to prevent in-hospital transmission. Unvaccinated infants are prone to developing severe complications of measles; therefore, those with respiratory deterioration need to be transferred in an early stage to the PICU.

**References**

Table 1: The demographics of the three cases

<table>
<thead>
<tr>
<th>Cases</th>
<th>Case One</th>
<th>Case two</th>
<th>Case three</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
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<td>9 months</td>
<td>11 months</td>
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<tr>
<td>Gender</td>
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<td>Female</td>
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<td>Comorbidities</td>
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<td>Trisomy 21, Operated VSD</td>
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<td>Duration of positive pressure ventilation</td>
<td>1 day (Non-invasive Ventilation)</td>
<td>7 days (Invasive ventilation)</td>
<td>1 day NIV</td>
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<td>Length of PICU stay</td>
<td>1 day</td>
<td>10 days</td>
<td>1 day</td>
</tr>
<tr>
<td>Complications</td>
<td>ARDS, secondary bacterial infection</td>
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VSD = ventricular septal defect; NIV = non-invasive ventilation; PICU = paediatric intensive care unit; ARDS = acute respiratory distress syndrome.