Measles in HIV-infected children in southern Africa

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Abstract

In recent years, southern Africa has experienced a widespread measles outbreak. Given the high human immunodeficiency virus (HIV) prevalence in the region, the particular features of measles in HIV-infected individuals are of interest to clinicians, especially as regards children, as are measles immunisation strategies for this population. This review discusses a case of severe measles in an HIV-infected child in Botswana, focusing on its implications for clinical case management in Botswana and similar settings and for policies on measles immunisation.

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Introduction

In recent years, southern Africa has experienced a substantial and persistent outbreak of measles, with the greatest impact seen in children. As southern Africa is also the region of the globe with the highest prevalence of human immunodeficiency virus (HIV), a large proportion of measles infections in the recent outbreak has been seen in HIV-infected children, including in Botswana, one of the world's highest paediatric HIV prevalence settings, where approximately 3% of all children under age 18 years are HIV infected.[1]

Measles presents both diagnostic and therapeutic challenges to physicians when seen in children with HIV infection, including atypical presentations[2] and severe illness.[3,4] A high clinical suspicion for measles is needed when caring for HIV-infected children during a measles outbreak, as children with HIV may not develop the typical generalised, descending erythematous rash classically seen with measles[5] and are more likely to have serologically unconfirmed measles, secondary to a lack of immunoglobulin M response.[3] Indeed, most of the thousands of clinical measles cases in the recent southern African outbreak are serologically unconfirmed, as obtaining a serological diagnosis is both logistically and resource-wise difficult in the public health systems in the region to which the vast majority of cases present.

For national authorities, the negative effect of HIV infection on achieving and maintaining humoral immunity[6] against measles in HIV-infected children[7] presents a challenge to the high levels of herd immunity (over 90%) required to prevent measles transmission and necessitates consideration of immunisation policies.

This review discusses a particularly challenging recent case of severe measles in an HIV-infected child in Botswana, focusing on the implications of such cases both for the optimisation of clinical case management of measles in HIV-infected children in Botswana and similar settings and for policies on measles immunisation.

Clinical case

LB, an eight-year-old girl, was diagnosed with HIV infection in July 2009 and initiated on Botswana's first-line antiretroviral therapy (ART; zidovudine, lamivudine and efavirenz for a child her age) in August 2009, secondary to substantially advanced clinical stage (unexplained severe malnutrition; z scores for weight and height for age both less than minus three) and severe immunosuppression (CD4 313 cells/mm^3 or 11% two weeks before ART initiation). LB had been improving clinically as well as immunologically after six months on ART (CD4 852 cells/mm^3 or 18%). While initially adherence to ART was excellent, over the last few months prior to measles diagnosis it had become less optimal. Nonetheless, LB's last viral load (VL) prior to presenting

Table I: CD4 and viral load trends at three-month intervals on antiretroviral therapy

Laboratory results	July 2009 (baseline)	October 2009	January 2010
CD4 (cells/mm^3)	313	802	852
CD4 %	11	14	18
VL (copies/ml)	---	5 500	< 400

with measles (January 2010) remained undetectable (less than 400 copies/ml) and CD4 was robust (852 cells/mm^3; see Table I). Both her weight (18 kg) and height (115.6 cm) remained below minus three standard deviation for weight and height for age at the time of measles diagnosis.

In March 2010, LB presented to an outside clinic with rash, conjunctivitis and fever, and was clinically diagnosed with measles. No serology was sent, and no record is available of treatment prescribed at the local clinic. Her rash and conjunctivitis resolved, but she presented a week later to the Princess Marina Hospital in Gaborone, Botswana, with persistent fever, nonproductive cough, right-sided chest pain and moderate shortness of breath. On examination she was found to be febrile (38°C), tachypnoeic (respiratory rate 48), hypoxic (O_2 saturation 89% on room air) and with a chest examination suspicious for left-sided pneumonia. Intravenous penicillin and vancomycin were started. Appropriate laboratory investigations were ordered, including blood cultures. She was placed on oxygen via face mask, which brought and maintained her oxygen saturation at 100%. She remained febrile and tachypnoeic and required oxygen throughout the first day of admission.

The following day, a chest film was obtained, which showed bilateral homogenous opacities sparing only the apices (see Figure 1). Complete blood count was without substantial abnormalities, while electrolytes demonstrated severe hyponatraemia (sodium 119) and liver functions were notable for mildly elevated transaminases. The admitting clinical team made an assessment of extensive bilateral lobar pneumonia and penicillin was changed to cefotaxime. Vancomycin was continued and the patient was kept on oxygen.

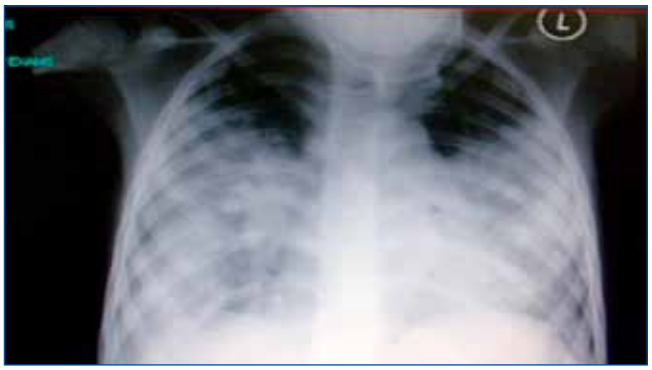

Figure 1: LB's chest x-ray, demonstrating bilateral homogenous opacifications

On her third day of admission, LB's condition deteriorated. Mechanical ventilation was not available due to limited capacity in the intensive care unit. During the early hours of hospital day three, LB's condition showed further rapid decline and cardiopulmonary resuscitation was initiated, including epinephrine (0.1 mg/kg 1:1 000) as per protocol. LB failed to respond to resuscitation attempts and expired on hospital day three.

After 72 hours, the blood culture that was drawn on admission grew *Staphylococcus aureus* sensitive to vancomycin, erythromycin and amikacin.

Discussion

This case demonstrates several features of note when considering measles infection in an HIV-infected child in low-resource settings such as Botswana.

Deaths due to measles are usually caused by bacterial or viral complications of measles, which may occur well after clinical measles has resolved.[3] Bacterial pneumonia, the presumed cause of death in our case, is a common complication of measles and can be associated with bacteraemia or severe acute respiratory distress syndrome, leading to a need for mechanical ventilation[8] and high mortality.[4] Indeed, measles-infected patients have been found to have several-fold higher rates of bacteraemia than non-measles infected, comparably ill general paediatric patients.[9] HIV-infected patients may experience pneumonitis and encephalitis more frequently with measles than HIV-uninfected patients, with higher rates of complications and mortality.[10] Neurological sequelae of measles, including subacute encephalitis, subacute sclerosing panencephalitis and myelopathy, have also been reported in HIV-infected patients.[5]

HIV infection is likely a risk factor for severe illness with measles, as well as for higher morbidity and case-fatality rates (CFRs) than for HIV-uninfected patients. Older paediatric studies in the Democratic Republic of the Congo (DRC) and Zambia showed CFRs of 31% vs. 28% and 28% vs. 8.3% in HIV-infected vs. HIV-uninfected children.[11-13] A more recent Zambian study found HIV to be a risk factor for mortality in children admitted to hospital with measles, showing an overall CFR of 12.2%, with the presence of HIV doubling the odds of death.[3] HIV-infected children are also more likely to have severe disease, require admission to a hospital and have longer hospital stays than HIV-uninfected

children.[13] Immunosuppression, when present, also further increases the risk of severe measles and poor clinical outcome in HIV-infected children.[3]

Malnutrition also likely plays a role in the risk of severe measles and poor measles outcomes. At the time of ART initiation, our patient was severely malnourished presumably as a complication of HIV infection. While she had experienced some improvement in nutrition status during her several months on ART, she remained severely malnourished at the time of measles infection. Malnutrition is known to increase susceptibility both to measles infection[14] and to severe measles, including higher CFRs,[15,16] in both HIV-infected and HIV-uninfected patients.[10] Stunting has a known association with measles infection in HIV-infected children, as does wasting.[13]

Data from several sub-Saharan African settings have shown that CFRs remain high, despite more than 85% of measles patients' seeking medical care.[17] This underscores the importance of health care workers' maintaining a high clinical suspicion for measles-related complications such as severe pneumonia, which can be especially challenging to manage in low-resource settings. Many such settings lack adequate intensive care resources, including mechanical ventilation, to care for seriously ill children with measles complications, making prompt medical management with effective antibiotics particularly crucial. Lack of available mechanical ventilation likely played a role in our patient's ultimate outcome, and improving capacities to care for critically ill children in low-resource areas deserves attention.

How to achieve proper immunisation of HIV-infected children and maintenance of the very high levels of measles herd immunity required to prevent community-level measles transmission in settings of high HIV prevalence is of great interest. Standard vaccination approaches may result in higher rates of both primary and secondary vaccine failure in HIV-infected children.[5,18,19] Once infected with measles, HIV-infected children may have a prolonged infectious period and viral shedding, increasing the risk of transmission to other susceptible groups and potentially perpetuating outbreaks.[18,20,21]

The recent measles outbreak in southern Africa, despite high levels of measles vaccination coverage at country level across the region, suggests both deficiencies in national measles immunisation strategies and the particular contribution of high HIV prevalence mentioned above.

In Botswana, the current policy is for all children to receive a single measles monovalent immunisation at age nine months, with no booster. Yet, data suggest that 15-20% of children given measles vaccine at age nine months fail to seroconvert compared with much lower rates of failed seroconversion in children immunised between 13 and 18 months, as low as 6-8% in one study.[22] In HIV-infected children in the DRC and Thailand, seroconversion after measles immunisation at nine months has been shown to be as low as 57-65%.[20] Several small studies have shown that HIV-infected children who do not develop antibodies after the first measles vaccine often do not develop antibodies upon revaccination.[20] While HIV-exposed and HIV-uninfected children do have similar high rates of serocoversion (90-95%) when revaccinated after primary immunisation failure, only 64% of HIV-infected children do.[19] Accordingly, a second measles vaccine would be expected to deliver a substantial boost in herd immunity and provide better protection to all children, including HIV exposed/uninfected, HIV infected and HIV uninfected. It is likely to be of particular importance for HIV-infected children, making such an approach a priority for HIV-prevalent settings.

In 2009, the World Health Organisation (WHO) recommended that all countries attempt to reach all children with two doses of measles vaccine, with the highest priority placed on timely delivery of the first dose.[23] Where risk of measles transmission is high, the WHO recommends the first dose at nine months with a second dose at 15-18 months of age as part of routine immunisation schedules for countries that regularly achieve over 80% first-dose coverage of measles immunisation;[23] for infants infected perinatally with HIV, even immunisation at age nine months may be later than optimal, as perinatally infected infants may possess inadequate levels of maternal anti-measles antibody at birth and through the first nine months of life, and are more likely to acquire measles before the first immunisation at nine months than other infants.[24]

In 2008, 94% of one-year-old children in Botswana had received one dose of measles vaccine.[25] In response to the recent measles outbreak and the above-mentioned concerns, Botswana is currently in the process of revising its national immunisation policy to include a second measles immunisation for all children at age 18 months. A similar strategy should be a priority for other resource-limited settings where high coverage of the first measles dose has been achieved.

More information is needed on the risk factors for severe measles in HIV-infected children, as well as on the optimal inpatient management of severe measles and its complications, including aspects of management that may be unique to HIV-infected

children. Management includes clinical decisions such as choice of empirical antibiotic for measles-associated pneumonia; little data currently exist in this regard. Specific studies along these lines are planned for paediatric populations in Botswana. Their data will assist local health care professionals and national authorities alike, both in further refinements to the approach to measles management in HIV-infected children and in the optimisation of public health measures necessary to control this ancient and relentless foe.

Declarations

The authors declared no conflict of interest.

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