

## ILLUSTRATIVE CASE

# Timing Is Everything: Recurrent Infections and Failure to Thrive in an Infant

Amy M. DeLaroche, MBBS, Nirupama Kannikeswaran, MD, Helene Tigchelaar, MD

## CASE

A 6-month-old African American boy presented to the emergency department (ED) with a rash first noted on his face, spreading to his torso and extremities over 2 days. He had no history of fever or new exposures, and the rash appeared to be pruritic. A review of systems was positive for a slight cough and increased work of breathing but was otherwise negative. Born full term via normal spontaneous vaginal delivery at 2466 g (2nd percentile), he was exclusively breastfed and immunized, with no allergies. His past medical history was significant for “episodes of wheezing,” without a formal diagnosis of asthma. A circumcision was his only surgical history. He had oral candidiasis and diaper dermatitis at 2 weeks of age, with no chronic illnesses; however, review of his electronic medical record revealed 3 hospitalizations and several ED and outpatient clinic visits.

Hospitalized twice at 4 weeks of age for projectile vomiting associated with apnea, cyanosis, and seizure-like activity, he was then readmitted at 5 months of age for multifocal pneumonia with dehydration secondary to enteritis. After these 3 inpatient stays and outpatient evaluations by the neurology, pulmonology, and gastroenterology services for emesis, paroxysmal upper and lower extremity movements, and apnea, he received a diagnosis of gastroesophageal reflux disease, for which he received trials of 2 antireflux therapies. Throughout these encounters, his weight remained in the second percentile.

Vital signs in the ED were as follows: temperature of 38.0°C rectally, heart rate of 120 to 148 beats per minute, respiratory rate of 36 to 60 breaths per minute, blood pressure 114/63 mm Hg, and oxygen saturation 88% on room air, which improved to 100% on 2 L of oxygen through a nasal cannula. His weight was 6.3 kg (<2nd percentile). A complete physical examination was notable for clear rhinorrhea, tachypnea, bilateral intercostal retractions with accessory muscle use and a prolonged expiratory phase, a diaper rash, and a generalized maculopapular eruption. Intravenous access was established, and he was started on maintenance intravenous fluids. He was given 1 dose of acetaminophen for his fever. A capillary blood gas showed mild lactic acidosis with a pH of 7.392, pCO<sub>2</sub> of 35.8 mm Hg, HCO<sub>3</sub> of 21.3 mEq/L, base excess of -2.6 mEq/L, and a lactate of 2.5 mmol/L. His complete blood cell count showed a white blood cell count of 7.2/mm<sup>3</sup>, hemoglobin 10.2 g/dL, hematocrit 33.1%, and a platelet count of 239/mm<sup>3</sup>. The differential on his complete

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Address correspondence to Amy M. DeLaroche, MBBS, Department of Pediatrics, Division of Emergency Medicine, Children's Hospital of Michigan, 3901 Beaubien St, Detroit, MI 48201. E-mail: [adelaroc@dmc.org](mailto:adelaroc@dmc.org)

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*Department of Pediatrics,  
Division of Emergency  
Medicine, Children's  
Hospital of Michigan,  
Detroit, Michigan*

blood cell count was normal except for lymphocytopenia ( $3.2/\text{mm}^3$ ). Electrolytes, glucose, and creatinine were within reference range, whereas the blood urea nitrogen, calcium, albumin, and total protein were low at 2 mg/dL, 8.0 mg/dL, 3.8 g/dL, and 7.5 g/dL, respectively. A chest radiograph was obtained (Fig 1), which demonstrated multifocal parenchymal airspace disease consistent with pneumonia. He was started on azithromycin and clindamycin for coverage of both atypical and aspiration pneumonia and admitted to the pediatric floor. Upon admission, an immunodeficiency disorder was considered in the differential diagnosis because of the history of recurrent pneumonia and failure to thrive. Thus, as part of the initial evaluation, an HIV test was ordered.

**Question:** Why should HIV be included in the initial evaluation of children with clinical concern for an immunodeficiency disorder?

### Discussion

Human immunity results from a complex interplay between the innate and adaptive immune systems, in combination with protection afforded by both anatomic and physical barriers.<sup>1</sup> Disruption of these processes and structures leads to an immune deficiency, categorized as either



**FIGURE 1** Chest radiograph demonstrating multifocal pneumonia.

primary or secondary.<sup>1</sup> A primary immunodeficiency, which broadly includes antibody, T-cell, phagocytic, and complement disorders, stems from a genetic defect.<sup>2</sup> Conversely, a secondary immunodeficiency is commonly attributed to barrier defects (eg, burns), underlying systemic disease (eg, HIV), or immune-mediating medications (eg, corticosteroids).<sup>1</sup> Primary and secondary immune deficiencies can present similarly; however, secondary immune deficiencies are more common in children.<sup>1</sup> Thus, HIV should always be excluded as part of the initial evaluation for primary immunodeficiency.<sup>1,3</sup>

### CASE CONTINUATION

The HIV antigen/antibody combination test was reactive, and a subsequent HIV Western blot was positive. The initial ultrasensitive HIV viral load was 1 017 379 RNA copies per milliliter. A bronchoscopy with bronchoalveolar lavage led to a diagnosis of *Pneumocystis jiroveci* and a respiratory culture demonstrating rare *Pseudomonas aeruginosa*.

**Question:** What is the epidemiology of mother-to-child transmission (MTCT) of HIV in the United States, and why does this clinical problem persist?

### Discussion

HIV is the most common severe acquired immunodeficiency in the United States, affecting ~1.2 million adolescents and adults.<sup>4</sup> In 2010, the incidence of HIV was 4 times higher in men than in women; however, 20% of new infections occur in women, with 84% of women contracting HIV through heterosexual contact.<sup>5</sup> Because women often contract HIV during their childbearing years,<sup>5</sup> 91% of pediatric HIV results from perinatal transmission.<sup>6</sup>

Perinatal transmission of HIV, which peaked in 1991 at 1650 cases in that year, occurs during pregnancy, during labor and delivery, and in the postpartum period via breastfeeding.<sup>7</sup> Various policies centered on the prevention of MTCT of HIV, recognized as a significant public health issue, were implemented in the 1990s.<sup>7</sup> These policies, which included early diagnosis and provision of antiretroviral therapy combined

with cesarean delivery when indicated and breastfeeding abstinence, resulted in a 95% reduction in the incidence of perinatal HIV in the United States.<sup>7</sup> Although this is a remarkable public health achievement, ~164 infants were born with HIV in the United States in 2010.<sup>8</sup> As with HIV among adolescents and adults,<sup>9</sup> African American children are overrepresented, accounting for 65% of these diagnoses.<sup>10</sup>

Elimination of perinatal HIV in the United States is defined by the following 2 goals: an MTCT rate of <1% among HIV-exposed infants and an incidence of <1 infection per 100 000 live births.<sup>7</sup> To achieve these goals, prevention in the United States centers around the Perinatal HIV Prevention Cascade, which includes primary prevention, preconception and prenatal care, universal prenatal HIV testing, antiretroviral prophylaxis, cesarean delivery as indicated, breastfeeding avoidance, and comprehensive clinical care for the mother and child.<sup>7,8</sup> Unfortunately, missed opportunities are identified in 74% of infected infants.<sup>7</sup> The majority stem from incomplete adherence to the prevention cascade secondary to various social and systemic barriers, such as poverty, maternal mental health problems, and underresourced health departments.<sup>7,8</sup> However, continued MTCT of HIV may also result from events occurring outside the cascade, such as seroconversion during pregnancy or breastfeeding, which accounted for 8% of cases reported between 2005 and 2010.<sup>8</sup> Thus, although elimination of MTCT of HIV is an achievable goal, prevention efforts continue to be undermined by complex problems related to delayed maternal diagnosis and insufficient antiretroviral prophylaxis.<sup>8</sup>

To facilitate timely maternal diagnosis, the current standard of care includes routine opt-out HIV testing for all women in early pregnancy.<sup>11,12</sup> Consequently, ~93% of women are tested at least once during pregnancy.<sup>13</sup> Repeat testing in the third trimester, performed in less than one-quarter of patients,<sup>14</sup> is recommended only in certain high-risk jurisdictions and circumstances.<sup>11,12</sup> Reliance on risk-based HIV testing in the third trimester is

problematic, however, because 25% of new HIV infections are found in patients with no clear risk factors.<sup>11,15</sup> As highlighted by our case, timely assessment and clear documentation of maternal HIV status in the newborn's medical record is imperative because early initiation of antiretroviral therapy, within 6 to 12 hours after birth, is recommended for effective prevention of perinatal transmission.<sup>12</sup> Given that 27% of mothers of HIV-infected infants receive their diagnosis after delivery,<sup>10</sup> repeat testing in the third trimester should be considered for all women and can easily be performed at delivery or in the immediate postpartum period.<sup>12</sup>

**Question:** How do infants with HIV present, and what is the recommended initial diagnostic test for infants and children?

### Discussion

Largely contracted in the peripartum period, pediatric HIV may have an acute or gradual presentation followed by an accelerated course compared with adults.<sup>16,17</sup> The majority of infants with perinatal HIV present within the first year of life, commonly by 5 months of age.<sup>18</sup> Although ~20% remain asymptomatic in this period, the same is true for only 6% of children by 5 years of age.<sup>18</sup>

HIV is a multisystemic disease<sup>16</sup> whose clinical manifestations can be variable, including fevers, lymphadenopathy, organomegaly, respiratory tract infections, recurrent otitis and sinusitis, hypotonia, and developmental delay.<sup>17</sup> Although the acute retroviral syndrome is rare in infancy, there is typically an asymptomatic or mildly symptomatic period lasting months.<sup>16</sup> This period is noted in our case, with a history of failure to thrive, enteritis, and recurrent mucocutaneous findings, all of which are common clinical features of children with HIV.<sup>17</sup> This mildly symptomatic period typically ends as it did for our patient: AIDS, with *Pneumocystis jiroveci* being the most common AIDS-defining illness.<sup>16,17</sup>

To render a diagnosis of HIV in children <24 months of age, antibody assays are generally not recommended because children in this age group may have

persistent maternal antibodies.<sup>12</sup> Rather, direct virologic tests, including HIV DNA and HIV RNA polymerase chain reaction, are preferred.<sup>12</sup> The specificity of both of these tests is 100% by 1 month of age, with an equivalent sensitivity at 3 months of age.<sup>12</sup> Two positive virologic tests are considered diagnostic.<sup>12</sup> In children >24 months of age, diagnosis rests on an HIV-1/2 antigen/antibody combination immunoassay confirmed by an HIV-1/HIV-2 antibody differentiation immunoassay.<sup>19</sup> Upon diagnosis, infants should immediately be referred to a multidisciplinary clinic because early initiation of combination antiretroviral therapy hinders disease progression and improves growth, neurocognitive development, and mortality.<sup>20,21</sup>

### CASE RESOLUTION

Additional history revealed that although the patient's mother had received prenatal care, she had switched health care providers during her pregnancy. She was reported to be HIV negative based on testing conducted in early pregnancy, but these records could not be obtained. Third trimester HIV testing was not performed. This patient had a prolonged 25-day hospital stay during which he gained 220 g yet remained below the first percentile for weight. He completed therapy for *Pneumocystis jiroveci* and *Pseudomonas aeruginosa* pneumonia complicated by rhinoviral, enteroviral, and adenoviral infections. He was also started on antiretroviral therapy including zidovudine, lamivudine, and lopinavir/ritonavir, with improvement in his viral load to 14 172 RNA copies per milliliter at the time of discharge.

**Question:** Had a secondary immunodeficiency disorder been excluded, is there a framework to aid clinicians with the initial approach to primary immunodeficiency disorders?

### Discussion

A primary immunodeficiency, which encompasses >180 specific diagnoses,<sup>1</sup> affects ~1 of every 2000 children in the United States.<sup>22</sup> However, the exact prevalence varies with the specific diagnosis: Milder disease, such as immunoglobulin A deficiency, occurs in 1

in 500 children, whereas serious forms such as severe combined immunodeficiency are seen in >1 in 100 000 children.<sup>2</sup> Often diagnosed in childhood,<sup>23</sup> the overall incidence of primary immunodeficiency is greatest in children <5 years of age.<sup>24</sup> Thus, although certain specific diagnoses may be rare, collectively, primary immunodeficiencies are not an uncommon pediatric problem.<sup>2</sup>

Unfortunately, rendering a diagnosis of primary immunodeficiency in children is difficult, and diagnostic delay is well documented.<sup>24</sup> Primary immunodeficiencies tend to present as 1 of 8 clinical presentations: recurrent ear, nose, and throat infections; failure to thrive from infancy; recurrent pyogenic infections; unusual or unusually severe infections; recurrent infection with the same type of pathogen; autoimmune or chronic inflammatory disease; characteristic combinations of clinical features suggestive of an eponymous syndrome, such as Chediak-Higashi syndrome; and angioedema.<sup>25</sup> Although pattern recognition is the preferred approach to making a diagnosis of primary immunodeficiency,<sup>1,2</sup> variable clinical presentation and disease severity complicates this process.<sup>25</sup> Furthermore, the most common clinical presentation of primary immunodeficiency, recurrent respiratory infections, is also the hallmark of early childhood.<sup>1</sup> In fact, after evaluation, only 10% of children with a history of recurrent infection are diagnosed with primary immunodeficiency.<sup>1</sup>

To aid clinicians, the "10 Warning Signs of Primary Immunodeficiency" were developed through expert opinion and published by the Jeffrey Modell Foundation.<sup>26</sup> The presence of  $\geq 2$  "warning signs" should trigger diagnostic evaluation.<sup>27</sup> Unfortunately, the "warning signs" have been shown to have low sensitivity (23%) and specificity (63%) and failed to identify more than one-third of patients who ultimately receive a diagnosis of primary immunodeficiency.<sup>28</sup> If the diagnosis is called into question, a preferred starting point is to identify a history of serious, persistent, unusual, or recurrent infections.<sup>1</sup> This history, in combination with a family history of

primary immunodeficiency, use of intravenous antibiotics for sepsis, and failure to thrive, identified ~90% of T-lymphocyte, complement, and neutrophil or monocytic primary immunodeficiency in 1 cohort.<sup>29</sup> Family history is the most robust identifier of primary immunodeficiency.<sup>29</sup> This schema is particularly relevant to the pediatric hospitalist because careful review of growth parameters and specific inquiry into the family history when admitting a patient for intravenous antibiotics may help identify patients in need of additional investigation. Although various diagnostic approaches have been published,<sup>1,3,23,25,30</sup> a reasonable approach is to first obtain a complete blood cell count with differential, immunoglobulins, a lymphocyte subset, and complement levels.<sup>1,3</sup>

## CONCLUSIONS

Primary and secondary immune deficiencies can present similarly; however, secondary immune deficiencies, specifically HIV, are more common in children. Resulting from perinatal transmission, pediatric HIV persists in the United States because of complex issues resulting in delayed maternal diagnosis and insufficient antiretroviral prophylaxis. Although our case underscores the need for hard copies of maternal HIV laboratory results in the newborn's medical record, it also highlights the fact that third trimester HIV testing at delivery or in the immediate postpartum period can be a life- and cost-saving approach to identifying children not identified through standard preventive interventions. Thus, routine third trimester HIV testing should be considered in all women but is rarely performed. Pediatric hospitalists, in collaboration with their obstetric colleagues, can help address this gap in care by developing systems to ensure routine rapid HIV testing at the time of labor and delivery, with documentation of these results in the newborn's medical record. As perinatal HIV continues to largely affect a more challenging patient population, this systemic change in practice would serve to bring us a step closer toward eliminating MTCT of HIV in the United States.

## LEARNING POINTS

- HIV should always be excluded as part of the initial evaluation for an immunodeficiency.
- Third trimester HIV testing should be considered for all women in labor or in the immediate postpartum period as a step toward eliminating MTCT of HIV in the United States.
- Immunodeficiency should be considered when a history of serious, persistent, unusual, or recurrent infections is elicited.

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