Haemophilus influenzae Type b in an Immunocompetent, Fully Vaccinated ALL Survivor

abstract

A 7-year-old boy with a history of recurrent acute lymphoblastic leukemia (ALL), in remission, presented to primary care clinic after 2 days of progressive right hip pain with weight-bearing activities. He was otherwise asymptomatic at the time of presentation. Blood cultures revealed Gram-negative diplococci, which prompted an MRI that was significant for a hip joint effusion and femoral head bone marrow edema. The patient had no sick contacts and no significant past medical history other than ALL. The patient had been given all recommended childhood vaccinations. Arthrocentesis and needle biopsy of the femoral neck were not diagnostic for malignancy and revealed only mild hip joint inflammation, leading to a diagnosis of osteomyelitis. The organism in the original blood culture was identified as Haemophilus influenzae type b, β-lactamase negative. Review of the patient’s medical records showed a history of complete immunization to Haemophilus influenzae type b. An immunologic evaluation was made to determine if the patient retained immunity from his other vaccinations. Pathogen-specific antibody testing revealed detectable antibodies to polio but not measles, mumps, rubella, varicella-zoster virus, tetanus, diphtheria, pertussis, or hepatitis B. This loss of immunologic memory appears to be a rarely described side effect of ALL chemotherapy. There is currently no protocol to evaluate the immunologic memory of patients who underwent chemotherapy for ALL or to revaccinate them after their treatment. It is unclear whether the loss of immunologic memory is genuinely rare or is underdiagnosed because affected patients are protected by herd immunity.
Acute lymphoblastic leukemia (ALL) is the most common cancer in early childhood. Protocols for both the treatment and follow-up for ALL are well established and extremely successful, with nearly an 80% 5-year incident-free survival rate.\(^1\) It is also well established that both ALL and the requisite chemotherapy are immunosuppressive, which makes the patient more vulnerable to pathogens usually prevented by normal childhood vaccinations. However, after treatment of ALL, once a patient is considered immunocompetent, there is currently not an accepted protocol to evaluate antibody retention from prechemotherapy vaccinations or to revaccinate ALL survivors who completed their full course of childhood vaccinations before chemotherapy.\(^2\) This case report describes of a 7-year-old survivor of recurrent ALL who was found to have osteomyelitis caused by *Haemophilus influenzae* type b (Hib), for which he had been vaccinated. The patient was subsequently found to have no humoral immunologic memory to the majority of his childhood vaccinations.

**PATIENT PRESENTATION**

A 7-year-old boy with a history of recurrent ALL for which he had been in complete remission for >1 year presented to his primary care pediatrician’s clinic with a 2-day history of worsening right hip pain with weight-bearing activities. The patient’s mother reported that 6 days previously the patient had a single elevated temperature of 100.2°F, which resolved the same day, and he had since remained afebrile. Blood cultures in clinic revealed Gram-negative diplococci, and the patient was transferred to the hospital for admission and started on intravenous (IV) antibiotics.

The patient was initially diagnosed with ALL at the age of 2 years and was treated per chemotherapy protocol COG-AALL0331. He was then in first remission until he relapsed at 4 years of age. He received additional treatment per chemotherapy protocol COG-AALL02P2 and had been in remission for >1 year before this presentation. There was no recent history of nausea, vomiting, diarrhea, cough, ear pain, dysuria, weakness, malaise, confusion, or syncope. In addition, there was no recent history of travel or camping, no known sick contacts, and no known trauma. The onset of illness occurred during the summer, so there were no school or daycare exposures. Birth history was a term delivery with no complications, and there was no significant past medical history except for ALL and a femur fracture that healed after closed reduction and casting. Surgical history included only the insertion and subsequent removal of a port-a-cath. Family history is noncontributory, and the patient had received all recommended vaccines up to 18 months of age according to the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices recommended schedule (hepatitis B × 3; Hib × 4; diphtheria, tetanus, and pertussis × 4. Inactivated Polio Vaccine × 3; Mumps-Measles-Rubella × 1; and varicella-zoster virus [VZV] × 1). All primary vaccines were given >6 months before his diagnosis of ALL. VZV immunity was documented before initiation of chemotherapy, although anti-Hib antibody testing was not performed before chemotherapy.

On physical examination the patient was afebrile with normal vital signs. The physical examination was unremarkable except for tenderness to palpation in the right groin without warmth, swelling, or erythema. Range of motion at the hip was normal, although there was discomfort with extension and abduction of the right leg. The gait was antalgic, favoring the left side.

The complete blood count and manual differential were within normal limits. The urinalysis was normal, and the patient’s serum C-reactive protein was elevated at 7.0 mg/dL. An MRI of his right hip was performed, which showed a large right hip joint effusion and bone marrow edema of the femoral neck that was interpreted as suspicious for osteomyelitis and septic arthritis. Arthrocentesis of the right hip and bone biopsy of the femoral neck revealed no pathologic evidence of malignancy and minimally inflammatory joint fluid (3100 white blood cells per mm\(^3\)). Although cultures (performed after the initiation of antibiotics) were negative, osteomyelitis was presumed to be the cause of the bone marrow edema. After 6 days of improvement in the patient’s symptoms and a decrease in his C-reactive protein, the patient was discharged to home to complete 10 days of IV antibiotic therapy followed by another 32 days of oral therapy.

The pathogen on the initial blood cultures was identified as Hib. The patient returned to clinic, and titers were drawn to assess his immunity to previous vaccinations. The patient had negative serum IgG for VZV, measles, hepatitis B, tetanus, pertussis, and diphtheria, although he did still retain evidence of immunity to polio, with titers of 1:8 (polio 1), 1:64 (polio 2), and 1:128 (polio 3). He also had detectable *Haemophilus influenzae* antibodies 4 weeks after his initial presentation. Subsequent immune workup revealed normal quantitative immunoglobulins, normal lymphocyte subsets (normal CD3, CD4, CD8, and CD19, according to Harriet Lane normal values; and normal CD2, natural killer cells, CD45RA, and CD45RO according to reference laboratory standards), and normal lymphocyte proliferation in response to mitogens with absent quantitative response to tetanus antigen. A complete reimmunization schedule was undertaken with seroconversion to hepatitis B, hepatitis A, measles, VZV, pertussis, diphtheria, and tetanus.
DISCUSSION

ALL is the most common cancer of childhood. Over the past several decades, multidrug, combination chemotherapy regimens have become the standard of care for both initial and recurrent ALL, which has been related to a significant improvement in the 5-year survival rate for pediatric leukemia. Whereas aggressive therapy has drastically reduced the recurrence of childhood leukemia, aggressive suppression of the patients’ immune systems may cause a loss in humoral immunity among children who have survived ALL. Multiple studies show various suboptimal levels of antibodies against routine childhood vaccines among ALL survivors. The mechanisms of defects after chemotherapy may include a deficiency of both naive and memory T-helper cells, as well as a lack of circulating antibodies. The intensity of chemotherapy also seems to be an important factor in loss of immune memory. Ek et al. described a cohort in which 53% of patients undergoing standard therapy retained antibodies to tetanus, whereas no patients had detectable antibodies after high-intensity chemotherapy. There is also some evidence that revaccination is effective at restoring protective levels of antibodies among primary ALL survivors whose adaptive immunity was compromised after chemotherapy, suggesting a revaccination protocol may be warranted. Although revaccination protocols already exist for bone marrow transplant recipients, there are currently no widely accepted protocols for testing humoral immunity in ALL survivors, revaccinating survivors, or instructing survivors to avoid exposure to possible sources of infection. In addition, no currently available data address the loss of immune memory or revaccination of survivors of relapsed ALL, for which higher cumulative doses of chemotherapy are given.

The possible defective humoral immunity in ALL survivors is of concern due to the recent reemergence of pathogens that had been largely eliminated in the United States, including Hib, pertussis, and measles. Vaccination rates for Hib remains high among children aged 19 to 35 months, with >90% of children in California completing their full course of vaccinations from 1999 to 2009. However, vaccination rates are not homogenous throughout states and exhibit both temporal and geographic clustering, which can leave some populations at especially high risk of local outbreaks. Therefore, at-risk children may not be able to rely on herd immunity for protection against vaccine-preventable diseases. Waning herd immunity is particularly worrisome for Hib, which, despite the existence of a vaccine that induces protective levels of antibodies in >99.5% of children younger than 5 years after 3 doses, continues to cause >8 million cases of serious illness and an estimated 370,000 deaths worldwide annually. Meningitis, the most common manifestation of invasive Hib, has an average case mortality of 5%, with 10% of survivors manifesting permanent neurologic sequelae. In the United States, however, the current Hib vaccination schedule has reduced the incidence of invasive Hib from 806 of 100,000 children under the age of 5 years in the prevaccination era to only 2.64 of 100,000 children in the post-vaccination era. These high rates of morbidity and mortality for Hib, paired with a high global disease burden, leads to a vital concern that ALL survivors be revaccinated if they lack humoral immunity from prechemotherapy vaccinations.

CONCLUSIONS

We present the first case we are aware of in which a fully vaccinated ALL relapse survivor presented with invasive Hib. This case prompted an evaluation revealing a lack of humoral immunity to nearly all previous vaccinations. Recent advances in the standard chemotherapy regimen for childhood ALL have significantly improved its 5-year survival rate. However, more aggressive chemotherapy regimens can compromise patients’ humoral immunity and can leave them without antibodies from previous vaccinations. Physicians treating survivors of ALL should consider the possibility of vaccine-preventable infections in their patient population. The case presented also indicates that additional research into the immunocompetence of ALL survivors may be indicated to determine if humoral immunity testing or revaccination should be routine practice.

REFERENCES

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