Arthus Reaction to Recombinant Hepatitis B Virus Vaccine

Hervey Froehlich1 and Rajeev Verma
Department of Pediatrics, Kaiser Permanente Medical Center, Fresno, California

A severe, local, inflammatory, late-phase reaction accompanied by skin necrosis occurred after an infant was given an intramuscular injection of recombinant hepatitis B virus vaccine. The clinical course and appearance of the rash were typical of an Arthus reaction. Although not identical to this case, prior reported cases of complement-mediated reactions occurring after hepatitis B virus infection or vaccination provide theoretical support for this diagnosis.

Recombinant hepatitis B virus (HBV) vaccine has been safe and immunogenic when given to infants and children. Severe adverse reactions to this vaccine have been reported only rarely worldwide. We report an unusually severe Arthus-type skin reaction that occurred after administration of recombinant HBV vaccine.

Case report. In mid-July 1992, after an uneventful pregnancy, a mother gave birth, by cesarean section, to a 3380-g female infant at a contract hospital of the Kaiser Permanente Medical Center in Fresno, California. The infant was born at term. Routine care of the newborn included intramuscular injection of 1 mg of vitamin K, and the infant was discharged from the hospital on day 2 of life. Diaper rash and blepharitis led to 2 office visits, but both conditions resolved before the newborn was brought to the clinic at age 16 days for a routine 2-week examination, the results of which were normal. The parents did not report, however, that the infant had been taking to the emergency department of a local children’s hospital 2 weeks previously because of projectile vomiting. At the time of the well-baby examination, the infant weighed 4520 g (50th percentile). The child was receiving Similac (Abbott Laboratories) with iron and was overfeeding. She had episodes of vomiting, for which oral rehydration solution was prescribed. Immunization was rescheduled for the next week.

The next day, however, the parents reported to another physician that the infant had been vomiting since the age of 2 weeks. No acute signs of dehydration were noted, and only mild anemia (hemoglobin level, 9.8 g/dL [98 g/L]) and thrombocytosis (platelet count, 472 × 10³ cells/µL [472 × 10³ cells/µL]) were present.

A contrast study of the upper gastrointestinal tract, performed 4 days after the visit to the second physician, showed moderate gastroesophageal reflux without obstruction, for which the primary physician prescribed metoclopramide hydrochloride (Reglan; Robins), which was given at a dosage of 0.11 mg/kg 3 times daily. The vomiting resolved.

Two days later, at the age of 73 days, the infant was returned to the clinic for the scheduled immunization. She received a second dose of 0.5 mL of HBV vaccine (Engerix-B) injected intramuscularly into the left deltoid muscle plus 0.5 mL of diphtheria-tetanus-pertussis (DTP) vaccine (Connaught Laboratories) injected intramuscularly into the left anterior thigh, 0.5 mL of Haemophilus influenzae type b conjugate vaccine (Praxis Biologics) administered intramuscularly to the right deltoid muscle.

Results of a 2-month well-baby examination, performed in mid-September at the Kaiser Permanente medical offices, were normal. The parents did not report, however, that the infant had been taken to the emergency department of a local children’s hospital 2 weeks previously because of projectile vomiting. At the time of the well-baby examination, the infant weighed 4520 g (50th percentile). The child was receiving Similac (Abbott Laboratories) with iron and was overfeeding. She had episodes of vomiting, for which oral rehydration solution was prescribed. Immunization was rescheduled for the next week.

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On awakening 3 h after vaccination, the infant was irritable, cried loudly, and was restless and inconsolable, refusing to take her bottle. The infant was returned to the physician’s office within 4 h after vaccination, appearing quite ill. Results of physical examination showed a pulse rate of 190 beats/min, a respiratory rate of 60 breaths/min with crying, blood pressure of 88/52 mm Hg, and an oxygen saturation level of 87% while breathing room air. Tachypnea and tachycardia were present. Distal extremities were pale and cool. A rash with tiny vesicles was seen on the left cheek and on the left lateral thigh next to the site of DTP vaccination. The infant cried persistently at a high pitch. The initial diagnosis was anaphylactic reaction secondary to DTP vaccination, and epinephrine was administered.
subcutaneously. At this point in care, the original bandage strip was removed from the vaccination site on the left deltoid muscle. A large 1.5-cm × 1.0-cm eschar (figure 1), which was not present contralateral to the vaccination site, was noted. The original bandage strips did not appear to have been removed by the parents.

Although the infant’s condition remained stable, she was elected transferred to the local children’s hospital, where she stayed for 4 days. At admission, the only abnormal laboratory results were a moderately elevated total leukocyte count (18.4 × 10^3 cells/L), an elevated level of immature granulocytes (14%), and mild hyperkalemia (5.8 mEq/L; 5.8 mmol/L). Culture of a specimen taken from the necrosis site yielded a few mild colonies of coagulase-negative staphylococci. The consulting plastic surgeon recommended local wound care without debridement. The Fresno County Child Protective Services office was contacted to perform an investigation, but no evidence of physical abuse was found.

After discharge, the infant was seen for evaluation and routine well-baby care 4 weeks after resolution of the reaction. Diphtheria and tetanus toxoids and acellular pertussis vaccine, H. influenzae type b vaccine, and oral poliovirus vaccine were given without complication. Diagnosis of the child’s condition indicated that she was “allergic” to HBV vaccine. The skin lesion eventually healed to keloid status. Results of a quantitative assay for antibodies to HBV surface antigen were negative (i.e., antibodies were undetectable by EIA), the total IgE level was normal, and no other allergies were noted.

**Discussion.** Recombinant HBV vaccine has been shown to be safe for adults and children. Local reaction to vaccination occurs at the injection site, but placebo-controlled studies have found that pain at the injection site was not more frequent among vaccinated patients than among those receiving placebo. Serious adverse effects have not included skin necrosis of the type reported here [1, 2].

Erythema nodosum has been reported to occur after vaccination with both serum-derived and recombinant HBV vaccine [3–7]. Because erythema nodosum has also occurred after natural infection, such erythema may be an autoimmune reaction to HBV surface antigen [6]. When the vaccine is administered intradermally, a clinically significant, persistent skin reaction occurs. In 1 study [8], after 6 months of follow-up, 67% of vaccinated patients had a visible macule, and 18% had an indurated lesion; biopsy specimens showed perivascular lymphohistiocytic infiltrates with various degrees of vasculitis.

These delayed hypersensitivity reactions to HBV surface antigen are uncommon and do not usually develop as intensely or rapidly as they did in the current case. An Arthus reaction better explains our finding. Although Arthus reactions have been studied extensively in animals and have been reported to occur only rarely after immunization, these reactions have been reported to occur after skin testing with tetanus toxoid and after administration of insulin [9, 10]. Arthus reaction typically occurs after intradermal injection (in contrast to our case, in which administration was done intramuscularly) of an antigen in a primed host who has high levels of CF antibody. In animals, the acute hemorrhagic inflammatory reaction reaches maximal intensity within 2–6 h, and the area may become necrotic [11]. The reaction occurs somewhat more slowly in humans, in whom it appears within 2–10 h and is maximized after 8–24 h [9, 10]. Acute inflammatory infiltrate of neutrophils, vascular damage, and endothelial cell proliferation are histologic findings. Deposition of immunoglobulin, complement, and fibrin occurs [11].

Arthus reactions are complement dependent and neutrophil dependent. Formation of immune complexes by the meeting of antigen and antibody in the vessel wall activates the classical Arthus reaction pathway. Fixed C3 fragments and the anaphylatoxins C3a and C5a are generated, increase vascular permeability, cause neutrophil invasion of the vessel wall, and induce hemorrhagic vasculitis [12]. A more familiar type of generalized Arthus reaction is serum sickness, which includes complement consumption, urticarial and morbilliform eruptions, fever, lymphadenopathy, synovitis, and proteinuria [13].

Another manifestation of vaccine-related Arthus reaction is atypical measles syndrome, which occurred among children who were vaccinated with killed measles vaccine and were subsequently infected with natural measles. These children had abrupt onset of fever followed by formation of a rash, and many of these children also had pneumonia and pleural effusion [14]. Samples obtained when these children underwent skin lesion biopsy showed a combined Arthus and delayed hypersensitivity reaction [15]. The children had a partial, but not protective, antibody response to killed measles vaccine;
natural measles induced an exaggerated and unbalanced antibody response that resulted in atypical measles syndrome.

We know of no prior reports in the biomedical literature of an Arthus reaction to recombinant HBV vaccine. This case is also unusual because of the presence of “satellite” skin rash at sites other than the vaccination site, the rapid onset of necrosis, and the absence of demonstrated antibody to HBV surface antigen. The occurrence of the rash at several sites and the degree of skin necrosis illustrate the severity of this reaction, which may have resulted from the vaccine leaking into or onto the skin at the time of administration. The absence of anti-HBV antibodies may link this Arthus reaction to that occurring in association with atypical measles syndrome, in which another nonprotective and, perhaps, CF antibody is formed after the first dose of vaccine has been administered in a separate injection; this antibody then causes an antibody-antigen-complex–mediated reaction.

Alternative hypotheses for the causes of this skin reaction might include another vaccine administered in a separate injection at the same site, contamination of either the individual vial or the entire lot of vaccine, or physical abuse of the child. However, our routine office practice, the secondary computer record of immunizations (which includes the site of injection and the lot number of the vaccine), and verbal corroboration by the nurse who administered the vaccinations all support the primary document showing that HBV vaccine was given intramuscularly at the skin site where the reaction occurred. Our medical group had purchased >1000 doses of the same lot of HBV vaccine and had been using it for several months before this episode occurred. No other unusual reactions were seen during this time, and the manufacturer reported no unusual side effects resulting from use of the vaccine lot. When the child’s pediatrician asked the parents about the reaction at the injection site, they denied removing the adhesive strip or applying heat, chemicals, or herbal remedies to the area. In addition, staff from the Child Protective Services office found no evidence of parental misbehavior.

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References