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Short Communication

Congenital Rubella Syndrome due to Infection after Maternal Antibody Conversion with Vaccine

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SUMMARY: We experienced a case of congenital rubella syndrome (CRS) due to infection after maternal antibody conversion with vaccine. The mother was immunized with rubella vaccine at 14 years of age, and was confirmed as having rubella-specific hemagglutination inhibition (HI) antibody at the 1:16 level both at ages 26 and 30 during preceding pregnancies. At the second week of the third gestation, her second child developed rubella. She did not suffer any symptoms, but was found to have rubella HI antibody at the 1:512 level at 9 weeks of gestation. She delivered a male baby weighing 2,545 g at 38 weeks of gestation. He had congenital pneumonia, patent ductus arteriosus, bilateral cataracts, sensorineural deafness, and periventricular calcification of the brain. The rubella-specific antibody was 1:512 by HI and 10.1 by IgM enzyme-linked immunosorbent assay. According to these observations, he was diagnosed as having CRS. The rubella virus genome was detected in the fluids of the vitreous body using RT-nested PCR. This case emphasizes the importance of double-dose immunization (once in infants and once in young adults) in order to obtain an adequate level of antibody with duration sufficient to ensure the prevention of CRS.

A 34-year-old Japanese woman was immunized with rubella vaccine at the age of 14 and then had been confirmed as having rubella-specific hemagglutination inhibition (HI) antibody with the 1:16 titer at the ages of 26 and 30 at the occasions of preceding pregnancies. At the second week of the third gestation, her second child (not immunized with vaccination) developed an illness clinically diagnosed as rubella. She did not suffer from any fever, rash, or lymphadenopathy during her last pregnancy, but was found to be producing the rubella specific HI antibody with titer of 1:512 at 9 weeks of gestation.

She delivered a baby boy weighing 2,545 g at 38 weeks and 2 days of gestation in 1996. At birth, the boy developed breathing difficulty and signs of infection (diagnosed as congenital pneumonia) as well as cyanosis. He was treated with drip infusion of antibiotics and eventually recovered from breathing difficulty within several days. He had an odd facial appearance, systolic murmur (diagnosed as patent ductus arteriosus (PDA) that required ligation on the ninth day of life), and 4 cm palpable hepatomegaly. He also had clouded corneas, squint, and bilateral cataracts. Although the eyes underwent operation at 3 months of age, the boy remains very weak in sight. In addition, he had bilateral severe sensorineural deafness (diagnosed by auditory brainstem response) with the necessity of hearing aids and periventricular calcification of the brain (revealed by CT). In general, the baby was retarded in both mental and physical development.

Laboratory examination of his blood serum at birth revealed Hb 14.6 g/dL, total white blood cell count 4,910/uL, decreased number of platelets (51,000/uL), total IgM 82 mg/dL, total IgG 691 mg/dL and CRP 6.63 mg/dL. In cerebrospinal fluids, no abnormality was found except for the high protein concentration (155 mg/dL). The titer of rubella-specific HI antibody was 1:512 and IgM enzyme-linked immunosorbent assay (ELISA) (Denka Seiken, Tokyo) titer was 10.1 (strongly positive). Serological signs of infection for toxoplasma and cytomegalovirus were not detected. According to these observations, the boy was diagnosed with congenital rubella syndrome (CRS). Although rubella virus was not isolated either from his throat swab, urine, or blood at birth, the rubella virus genome was detected in the fluids of the vitreous body using RT-nested PCR (1) when he underwent operation at 3 months of age.

Usually, rubella causes mild disease in young children with mild symptoms and good prognosis. However, infection during the early stage of pregnancy of the mother often induces serious congenital disorders of the infected fetus. Collectively called CRS, this condition affects mainly three organs: the ear (severe hearing loss), heart (PDA, PS [pulmonary stenosis], ASD [atrial septal defect], and VSD [ventricular septal defect]), and eye (cataract, glaucoma, retinopathy, and microphthalmos)(2). At the beginning of CRS research approximately 30 years ago, CRS due to re-infection of the virus was not considered, even if the booster effect of antibody production was often observed at asymptomatic re-infection (3). However, such a possibility had come to be considered feasible with the accumulation of case reports on "re-infection CRS" (4,5). As immunization programs expanded, CRS cases after vaccination had increased in number more than those after natural infection aimed to obtain primary immunity. So far, 30 cases of CRS after vaccination in Japanese patients have accumulated (unpublished data). However, all of them lack confirmation of the antibody conversion after vaccination or isolation of the virus and/or virus genome of the

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affected baby and thus are not clearly separable from the cases of primary vaccine failure. The rate of primary rubella vaccine failure in young adults (15-21 years old) is reported to be in the range of 0-2.2% for five strains of Japanese vaccines (6). Detection of the virus or virus genome in specimens from affected babies ensures more reliable diagnosis of CRS. Previous cases lacked virus and virus genome detection at birth (7). Here, we present a typical case of CRS after vaccination with a complete data set including history of vaccination, confirmation of the antibody, origin of infection, elevation of antibody in the mother, birth of baby with CRS phenotype, presence of IgM antibody, and the virus genome in the baby. This is the first case of CRS in Japan with confirmed antibody presence (twice) before infection after vaccination. A rubella immunization program began in Japan in 1977 and was initially applied to junior high school girls. When the immunization law was revised in 1994, the object of rubella immunization changed to 12 to 90-month-old children, both males and females (6). As a result, the presence of rubella antibody up to the childbearing age in vaccines has become questionable. In addition, no booster effect has been expected since the disappearance of rubella epidemic in Japan in the past 3 years (8). A recent study by Isomura et al. showed that rubella vaccination coverage rates were not significantly high: 71.2% at 12-90 months and 55.8% at 12-15 years in 1999 (9). Therefore, the present case emphasizes the importance of double-dose immunization (once in infants and once in young adults) with same timing as the present schedule using a single dose to achieve the adequate level of antibody with the appropriate duration of persistence required to ensure the prevention of CRS development. The purposes of double-dose immunization are (i) to immunize young adults who were not vaccinated at 12-90 months old, and (ii) to elevate of antibody titer until child-bearing age for sufficient protection from CRS due to re-infection.

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