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BRIEF REPORT

Vaccine Rubella: A Rare Cause of Post-transplant Hematopoietic Death, but a Major Public Health Problem

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We report the first case, to our knowledge, of a child who presented with severe zonal hepatic necrosis after allogeneic hematopoietic stem cell transplantation secondary to infection with the rubella virus RA27/3 vaccine strain.

Keywords. children; hematopoietic transplant; vaccine rubella.

Postnatal rubella infection usually causes mild exanthematic disease, frequently accompanied by adenopathy, occasionally by arthralgia, and rarely by liver failure. Since the introduction of rubella vaccine, the incidence of this infection has drastically decreased, especially in developed countries, and in the last decades only isolated cases of rubella infection have been detected in Spain. There are no published studies of rubella infection in immunosuppressed patients, a population in which live attenuated virus vaccines are contraindicated.

CASE REPORT

A 12-year-old boy was diagnosed with acute myeloblastic leukemia (AML) secondary to myelodisplastic syndrome (MDS) in September 2008. He did not have an human leukocyte antigen-identical donor, and allogeneic hematopoietic stem cell transplantation (HSCT) was performed in April 2009 from his haploidentical mother. The early post-transplant period was unremarkable. He achieved complete donor chimerism and was discharged from the hospital on day +16.

On day +31 post-transplantation, he was diagnosed with acute graft-vs-host disease (aGVHD) grade 2 with hepatic and intestinal involvement using compatible gut biopsy. Treatment with corticosteroids at 1 mg/kg/d was started, with good response.

On day +60 post-transplantation, he was admitted to the emergency department. He presented in poor condition with a Lansky score of 60%. He had diarrhea, generalized cutaneous exanthema, and conjunctiva jaundice. Laboratory findings showed a hemoglobin level of 11 gr/dL, platelets of 42 × 10^9/L, and white blood cells of 0.67 × 10^9/L. A bone marrow aspirate was performed, and he was in complete remission. Blood chemistry showed abnormal liver function with an aspartate aminotransferase (AST) of 439 U/L, alanine aminotransferase (ALT) of 578 U/L, gamma glutamyl transferase (GGT) of 1108 U/L, and bilirubin of 6 mg/dL (direct bilirubin: 3.5 mg/dL). Because of suspicion of recurrent aGVHD, the dose of corticosteroids was increased to 2 mg/kg/d, and treatment with intravenous cyclosporine was started. Despite treatment, the patient progressively got worse, with the appearance of abundant intestinal bleeding. A colonoscopy was performed, and he was diagnosed with aGVHD grade 4 with the presence of ulcers throughout the colon mucosa. Third-line therapy with extracorporeal photopheresis and subcutaneous etanercept was started. Cyclosporine was stopped due to the suspicion of thrombotic microangiopathy with severe arterial hypertension and renal failure. Liver function progressively improved, but his stool volume increased to more than 3000 mL per day with daily need for transfusions.

On day +80 post-transplantation, the patient's clinical condition rapidly deteriorated, and he went into fulminant hepatic failure (AST: 5766 U/L; ALT: 1767 U/L; and lactic dehydrogenase: 17993 U/L). He developed severe and refractory coagulopathy, hyperammonemia, and clinical acute encephalopathy with a decreased level of consciousness (Glasgow score: 6). He started with fever, hypotension, tachycardia, exanthema, and respiratory insufficiency, and finally he died on day +82 after transplantation. The family authorized the necropsy, which determined as the cause of death severe zonal hepatic necrosis of hemodynamic etiology. There were no signs of active GvHD in the liver, and microbiological analysis showed an isolated and surprising detection of rubella virus (RV) sequences of genotype 1A, similar to the vaccine strain RA27/3 by reverse transcriptase–polymerase chain reaction (RT-PCR) (Table 1). Total nucleic acids were extracted from samples, and a fragment of 875 bp including the region of the E1 gene, recommended by the World Health Organization (WHO) for RV sequencing, was amplified. Sequences were aligned and analyzed together with WHO reference strains to determine the genotype [2, 4]. The first positive result was obtained in the bone marrow on day +62

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Table 1. Detection of Vaccine Rubella Virus by RT-PCR

Date	25/03	1/07	14/07	16/07	21/07
Days pre/ post-transplant	–36	+62	+76	+78	+82
Blood	NA	NA	POS	NA	NA
Serum	NEG IgM– IgG+	NEG	POS	POS	POS Gen 1A IgM– IgG+
Bone marrow	NA	POS Gen 1A	NA	NA	NA
Intestinal biopsy	NA	NEG	NA	NA	POS
Spinal fluid	NA	NEG	NA	NA	NA
Urine	NA	NA	NA	NA	NEG
Liver biopsy	NA	NA	NA	NA	POS

Abbreviations: NA, not available; RT-PCR, real-time polymerase chain reaction.

post-transplantation, followed by serum or blood on days +76, +78, and +82 and liver and intestinal biopsy on day +82. The patient showed serological markers of preexisting immunity to RV (IgG positive, IgM negative) before transplantation, which remained on day +82. He was correctly vaccinated according to his community schedule, and his last dose of live virus vaccine was measles-mumps-rubella (MMR) at 4 years old. The patient had not received any vaccines since 1 year before because he was in the hospital as an inpatient during this time due to his poor social situation.

Secondary infection from a newly vaccinated person remains the only possibility to explain the presence of RA27/3 in the patient. He did not have a good social situation and was only accompanied by his mother, volunteer staff from the hospital, nurses, and doctors during his hospital admission, but we did not exactly know which person was the source of transmission.

DISCUSSION

Postnatal rubella infection usually causes mild exanthematic disease, frequently accompanied by adenopathy, occasionally by arthralgia, and rarely by hepatitis. Acute liver failure (ALF) secondary to rubella infection has been described in rare cases in immunocompetent children who've been properly vaccinated. A 2-year-old boy with IgG and IgM antibodies against RV who developed ALF with encephalopathy grade II and underwent orthotopic liver transplantation from a cadaveric donor, who has been in good health since then [1], and a 9-year-old girl who developed ALF needing urgent living-donor liver transplantation and died of multisystem organ failure despite intensive care. In this case, RV was isolated from the blood, urine, and liver [2].

Liver involvement by RV in adults is also relatively rare, and only isolated cases have been published, most of them many years ago [3].

However, the most severe consequence of this virus is congenital rubella syndrome (CRS) when the infection occurs in pregnant women [4]. It has also been described as an unusual cause of neonatal fulminant ALF in a 3-day-old preterm male infant affected by CRS. Enzyme-linked immunosorbent assay (ELISA) of both the baby and mother was highly positive for rubella IgM and IgG. Polymerase chain reaction testing for RV was also positive. Despite supportive treatment, he developed multi-organ dysfunction and died 4 days later. A postmortem liver biopsy was suggestive of diffuse hepatocyte necrosis [5]. Jaundice and other manifestations of acute hepatitis may occur in CRS. The hepatic lesions vary from mild hepatitis to ALF. The virus can be identified in the liver at necropsy or by biopsy. Hepatic dysfunction occurs at the same time as the onset of other symptoms of rubella. It is therefore suggested that liver injury in acquired rubella may be mediated by an immune mechanism [3].

In Spain, monovalent rubella vaccine was introduced in the late 1970s, when it was administered to 11-year-old girls in schools. In 1981, 1 dose of MMR combined with live attenuated vaccine was introduced in the regular immunization schedule at the age of 15 months for all children. In 1996, a second dose at 11 years was introduced. After 1999, this second dose was given to 4-year-old children, and so it is still in the current immunization schedule [6]. The high response rate to a single dose of rubella vaccine (≥95%) and the long-term persistence of protection in vaccines do not support a routine requirement for a second dose of rubella vaccine. However, based on the indications for a second dose of measles-containing and mumps-containing vaccines, a second dose of MMR is now offered in most countries [7]. Rubella vaccine contains live attenuated RA27/3 strain. In the case described here, there is no evidence of recent vaccination because the patient was in the hospital as an inpatient for the prior year due to his poor social position. The last dose of live virus vaccine received by the patient was MMR at 4 years.

Secondary infection from a newly vaccinated person remains the only possibility to explain the presence of RA27/3 in the patient. Pharyngeal excretion of RV occurs approximately 7 to 28 days after vaccination, with a peak of excretion by day 11. Evidence of excretion of the RA27/3 strain after vaccination has been recorded in immunocompetent people [8–10], either associated with clinical symptoms [9, 10] or not [8]. However, there has been no evidence before this case of horizontal transmission of the RA27/3 strain in a patient undergoing hematopoietic stem cell transplant. Administration of MMR vaccine to allogeneic stem cell–transplanted patients has been shown to be safe 2 years after transplantation in several studies [11], although a case of persistent rubella infection after erroneous vaccination in an immunocompromised patient with acute lymphoblastic leukemia has been reported [12]. The Infectious Diseases Society of America guidelines were created to provide primary care and specialty clinicians with evidence-based guidelines for active immunization of patients with altered immunity and their household contacts in order to safely prevent vaccine-preventable infections.

These guidelines recommend with a strong recommendation and moderate-quality evidence that healthy immunocompetent individuals who live in a household with immunocompromised patients should receive combined MMR vaccine without any risk [13]. However, in our case, the patient showed preexisting immunity against RV that was not able to prevent the infection. The patient showed an exanthema concomitant to the detection of RV RNA, which was accompanied by severe hemodynamic symptoms leading to ALF and death. ALF by rubella was probably the main cause of death.

In conclusion, it is important to consider that the immunosuppressed patient is at risk of contracting a live virus vaccine infection and to limit contact with rubella-vaccinated persons during the first month, which is the period of virus replication.

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