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CLINICAL LETTER

WILEY

Severe vaccine-acquired rotavirus infection in an infant with primary intestinal lymphangiectasia

To the Editor:

Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) is a monovalent oral live-attenuated vaccine derived from human rotavirus G1P[8].[1] It is specifically contraindicated for infants diagnosed with severe combined immune deficiency (SCID), with a history of intussusception or a history of uncorrected congenital malformation of the gastrointestinal tract.[1] However, in the absence of newborn screening for SCID, most undiagnosed infants with contraindications stated above are at increased risk of developing vaccine-acquired rotavirus infection. Several cases of severe gastroenteritis have been reported in infants with SCID when Rotarix was administered prior to diagnostic confirmation,[2] but no data are available contraindicating it for other immunocompromised hosts with conditions different from SCID.

We describe the first case of a previously asymptomatic infant who developed a severe vaccine-acquired rotavirus infection after receiving the first Rotarix dose, associating lymphopenia and hypoalbuminemia. This ultimately led to the diagnosis of primary intestinal lymphangiectasia (PIL), being SCID ruled out. The patient was a two-month-old full-term male infant, the first child of nonconsanguineous parents. The child had a good developmental curve and did not attend daycare. Twenty-four hours after Rotarix administration, he developed diarrhea that progressively worsened and resulted in weight loss and in eyelid and scrotal edemas. Hospital admission was required 7 days after vaccine administration. No growth retardation has been observed until he was vaccinated. He was transferred to our hospital 13 days after immunization, requiring 24 h of pediatric intensive care due to severe dehydration and significant electrolyte disturbances.

When he was first admitted to our hospital, he presented with severe lymphopenia (230/mm^3), hypoalbuminemia (1.2 mg/dL), and elevated faecal alpha-1-antitrypsin levels (7.71 U/g) with a profound decrease in IgG and IgA levels. The patient was placed on cotrimoxazole prophylaxis and gammaglobulin replacement therapy (Figure 1, Table 1). A complete immunological study was performed that showed normal results (Table 1). The patient's DNA was screened for genetic variants of genes related to primary immunodeficiencies (PIDs) using a next-generation sequencing-customized panel including 479 genes without pathogenic findings. A histological study of the intestinal biopsy showed lymphatic dilations suggestive of lymphangiectasia. Several studies were performed to rule out secondary causes of lymphangiectasia (cardiac evaluation, ultrasound, and intestinal barium tests). A multiplex PCR-based detection of 18 enteropathogens performed on stool samples [Allplex™ Gastrointestinal Panel Assays (Seegene, Seoul, South Korea)] only detected rotavirus on days 22, 29, and 37 after vaccine administration (Figure 1). PCR testing for herpesvirus in blood and intestinal biopsy were negative. The patient required prolonged parenteral nutrition, octreotide therapy (4 weeks), periodic infusions of albumin, and nitazoxanide therapy (3 days). The patient was required to fast for several days and received parenteral nutrition for several weeks, being re-fed progressively with a strict low-fat diet supplemented with fat in the form of MCT. The patient showed progressive improvement in digestive tolerance, which allowed the withdrawal of parenteral nutrition (Figure 1). The analytical parameters of lymphatic loss subsequently showed a clear trend towards improvement and normalized 14 months after the infection (Figure 1, Table 1). However, the patient needs to remain on this strict low-fat diet with MCTs in order to maintain an optimal serum albumin and lymphocyte count.

Genome segments coding for VP4, VP6, and VP7 structural proteins were amplified by PCR and sequenced from the stool sample obtained 22 days after Rotarix administration (lot AROLC991AB). Nucleotide and amino acid sequences were compared to those of Rotarix in the GenBank database. Lot AROLC991AB yielded an identical sequence to the Rotarix sequence for each of the three genes tested (VP4, VP6, and VP7) with the exception of three nucleotide and three amino acid substitutions (Table S1). Genome sequences from a stool specimen obtained 7 days apart were identical to the first sample.

We describe the first case of severe vaccine-acquired rotavirus disease in an infant vaccinated with Rotarix and diagnosed with PIL. Although administering this vaccine to patients with gastrointestinal malformations is contraindicated, PIL is exceptionally diagnosed before the age of two months[3]. Thus not administering Rotarix to these patients is an unlikely scenario. Patients with PIL presented with a predominant loss of CD4+ T cells[4]. Although the number of naïve CD4+ T cells is decreased, memory CD4+ cells are preserved and could have a role in preventing infections[4]. Naïve CD4+ cells are the predominant subset in infants, therefore they might be more susceptible to opportunistic and viral infections.

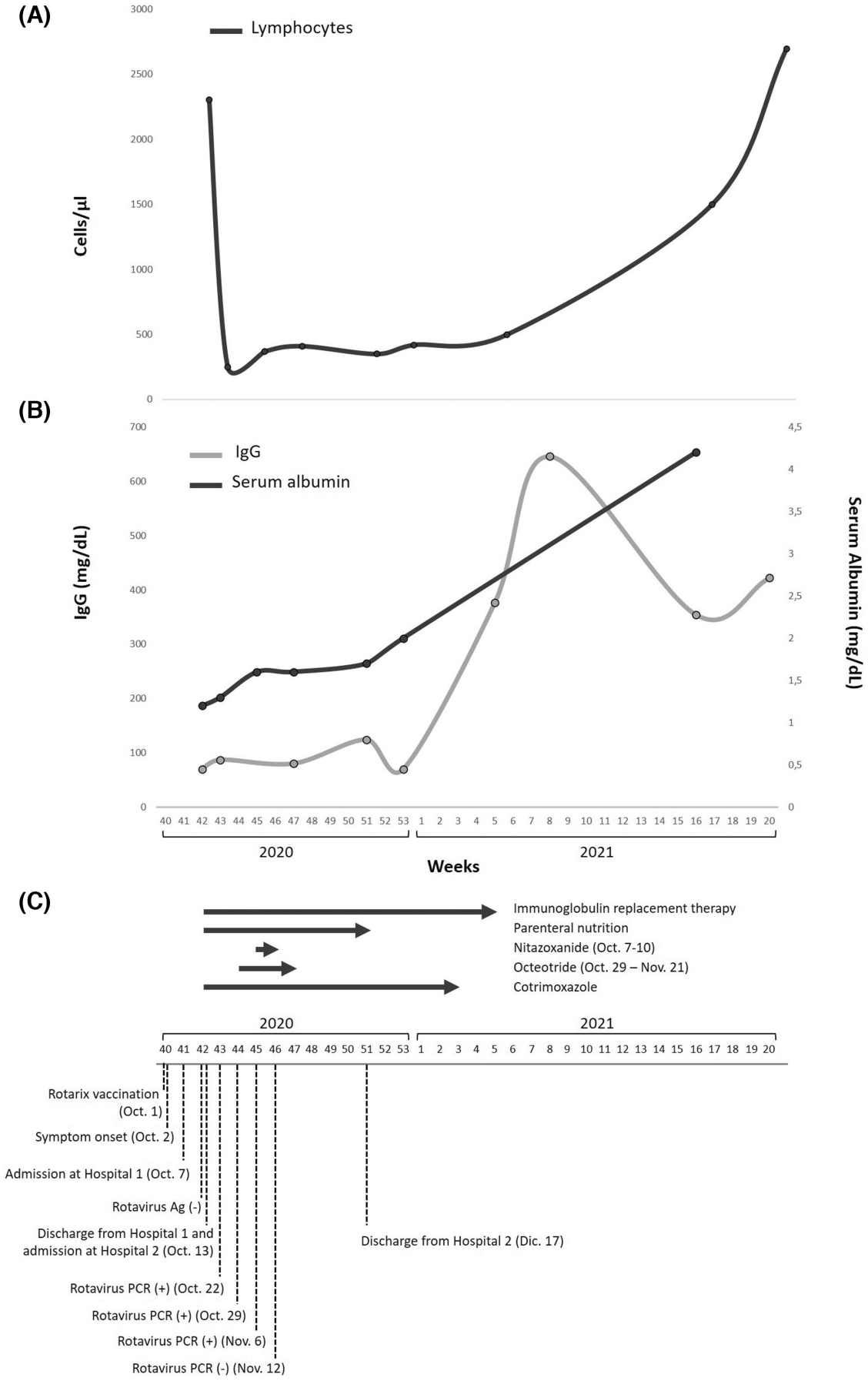

FIGURE 1 Lymphocyte count (A), IgG titers, and serum albumin (B) in our patient and their relationship with the clinical timeline (C)

Prasad et al.[5] recently published the clinical profile of 28 children diagnosed with PIL and observed that 10% of these children presenting with recurrent infections. Other authors have also reported severe and/or opportunistic infections, such as cryptococcal and pneumococcal meningitis, recurrent warts, varicella zoster, and bacterial sepsis, with a number of these patients dying due to the infection.[6]

Rotarix vaccine-derived G1[P8] strains have been globally described in infants around the time of their routine immunization.[7,8] This shedding has not been associated with an increase in gastroenteritis-like symptoms.[9] Our patient's stool samples (at 22, 29, and 37 days postvaccination) were persistently positive for rotavirus by quantitative reverse-transcription PCR, coinciding with clinical worsening, and leading to the diagnosis of PIL.

Prolonged shedding of vaccine strain rotavirus is also reported in infants with SCID, who usually require successful immune reconstitution to clear the infection.[2,10,11] The development of severe gastroenteritis after rotavirus vaccination could be the trigger that leads to a diagnosis of their underlying disease in infants with SCID[2] as we have observed in our case. Many of these children will require hospital admission.[2] In our patient, nitazoxanide was prescribed as this drug is able to reduce the duration of rotavirus disease in severe hospitalized pediatric patients.[12]

The G1[P8] strain detected in our patient was analyzed. Nucleotide sequencing and phylogenetic analysis of the VP4, VP6, and VP7 coding genes revealed very high nucleotide and amino acid identity rates between the study and the Rotarix strains, supported by high bootstrap values in the phylogenetic analysis (Figure S1). The high similarity to the Rotarix vaccine strain and the failure to detect other common enteric pathogens reassure the likelihood of infection caused by the vaccine-derived strain. Mutations F170L in VP4 and M202T in VP7 had been documented earlier for all described cases of Rotarix vaccine-derived strains and have caused acute gastroenteritis in infants with SCID (Table S2). It is plausible that the vaccine strain could have regained a pathogenic phenotype through these newly acquired mutations. Changes could be due to genetic drift occurring since the administration of the vaccine or because of the *in vivo* selection of minor variants already present in the vaccine[13].

Our case report highlights the risk of this vaccine in patients with PIL. The presence of other causes of lymphopenia different from SCID should be also considered in infants with severe gastrointestinal symptoms after rotavirus vaccination.

Key Message

To date, severe cases of vaccine-related rotavirus infection have only been reported in infants with severe combined immunodeficiency after immunization. We describe the first case of vaccine-related rotavirus gastroenteritis in an infant with intestinal lymphangiectasia.

TABLE 1 Immunological studies of the patient at diagnosis and during his clinical follow-up

	2.5 Months of age (14 days after vaccination)	7 Months	11 Months
Lymphocyte count	620/μL	1090/μL	2890/μL
Lymphocyte subsets (% of lymph CD45+)			
T CD3+	28% (173/μL)	67 (730/μL)	70(2023/μL)
T CD4+	14% (86/μL)	42(457/μL)	44(1271/μL)
T CD8+	7% (43/μL)	20 (218/μL)	20 (578/μL)
B CD19+	37% (230/μL)	23 (250/μL)	19 (549/μL)
NK CD16 + 56+	32% (198/μL)	7 (76/μL)	9 (260/μL)
CD4 subsets (% of CD4):			
CD4 + CD31 + CD45RA+ (RTE)	41%	68%	74%
CD4 + CD127low CD25+ (Treg)	14%	7%	8%
Proliferation test ConA; PHA; PWM; OKT3	Normal proliferation	Normal proliferation	
IgG	<70 mg/dL	599 mg/dL*	354 mg/dL
IgA	<7 mg/dL	<7 mg/dL	<7 mg/dL
IgM	24 mg/dL	33 mg/dL	31 mg/dL
TRECs (copies/punch)	50 (normal>8)		--------

Note: *Trough levels prior to immunoglobulin replacement therapy.

Abbreviatioins: ConA, concanavalin A; NK, natural killer cell; PHA, phytohemagglutinin; PWM. pokeweed-mitogen; RTEm, recent thymic emigrant; TRECs, T-cell receptor excision circles; Tregs, T regulatory cells.

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KEYWORDS

attenuated vaccine, intestinal lymphangiectasis, rotavirus

CONFLICT OF INTEREST

The other authors have no example conflicts of interest to disclose.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.