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MMRV Vaccine Associated Transient Neutropenia: Description of Two Cases

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Abstract

Post-vaccination neutropenia is not uncommon. The risk of thrombocytopenia following MMR vaccination is 1 in 30,000 to 1 in 40,000 vaccinated children. The clinical course of these cases is usually transient and benign.

Keywords: Transient neutropenia; Thrombocytopenia; Partial immunization; MMRV vaccine; MMRV adverse events

Introduction

Post-vaccination neutropenia is not uncommon. The risk of thrombocytopenia following MMR vaccination is 1 in 30,000 to 1 in 40,000 vaccinated children. The clinical course of these cases is usually transient and benign. The vaccine Priorix Tetra (MMRV) is a vaccine consisting of alive but attenuated measles, rubella, mumps, and varicella-zoster viruses. In Europe and North America, the vaccine, according to the immunization schedule, is administrated in two doses: at age of 13-15 months and, 4-6 years.

Case Report

In this study there are two children who developed a transient neutropenia related to Priorix Tetra vaccine injection (MMRV, GSK). The one of them, also had symptoms very similar to a wild type of measles virus infection, and thombocytopenia.

Case 1

The first case refers to a 17-month-old male child, born from normal pregnancy, delivered on term, regularly immunized and rarely sick. On May 18, 2017, at the age of 17 months, a MMRV vaccine was administrated (Priorix-Tetra, GSK). On May 30, he showed petechiae on his face and legs. On May 31, the platelet level was normal, but mild neutropenia was presented (absolute count 970 neutrophils). On June 13, neutrophils level went back to normal (2,400). There were neither IgG, nor IgM anti-Rubella. Anti-Measles antibodies were >300 UA/ml.

Case 2

The second case refers to an 18-month-old male child, born from normal pregnancy and delivered on term. The weight at birth was 3870 gr and the length 52 cm. During the first year of his life, he presented recurrent otitis and recurrent wheezing episodes, which were often requiring appropriate therapeutic interventions. Because of that, he could not get all vaccinations in the scheduled times. On August 24, 2017, at the age of 18 months, a MMRV vaccine was administrated (Priorix-Tetra, GSK). The next day, he showed fever that soon rose over 39°C and lasted until September 2, 2017 (9 days fever). Seven days after the injection of the vaccine MMRV, he presented conjunctivitis and a macular rash on the trunk and the limbs with some target elements. He was admitted to a pediatric unit from the 1st until the 7th of September 2017.

He had several examinations, some of which are summarized in the Table 1. Subsequently, during the hospitalization, a tipic morbilliform rash was developed on the face, which then progressed in the cranio-caudal direction and lasted until September 4, 2017. The number of neutrophils reached its minimum of 750 on the 9th day after vaccination. Thombocytopenia began on the 8th day after vaccination (98,000) and the level of white blood cells was almost halved compared to the previous value. After 17 days from the vaccination, neutropenia was not yet normalized (1,150 compared to 1,500, which is considered to be the minimum normal value). The lowest level of platelets was detected after 46 days from the date of vaccine administration (46,000). Regarding the specific antibody response, the IgG anti-rubella (60 IU/mL) and IgG anti-measles were detected (256 UA/ml), but the IgG anti-parotitis were absent. Therefore, the administration of the MMRV vaccine led to partial immunization.

Date	White Blood Cells	Neutrophils	Platelet
August 30, 2017	6,600	1,500	133,000
September 1, 2017	3,650	820	98,000
September 2, 2017	5,010	750	124,000
September 3, 2017	7,180	1,020	167,000
September 6, 2017	6,050	1,150	238,000
October 9, 2017	9,130	2,240	46,000

Table 1: Laboratory examinations, case 2.

Discussion

In this article there have been presented two cases of transient neutropenia related to Priorix Tetra vaccine injection (MMRV, GSK). Furthermore, one of them, also had symptoms very similar to a wild type measles virus infection, and thombocytopenia.

The hematological changes disappeared shortly afterwards. Neutropenia, usually defined as an absolute neutrophil count (ANC) below 1.5×10^9/L (1500/mm^3), encompasses a wide range of diagnoses, from normal variants to life-threatening acquired and congenital disorders. Neutropenia can be classified in mild neutropenia, with an ANC of 1,000-1,500/μL; moderate neutropenia, with an ANC of 500-1,000/μL; or severe neutropenia, with an ANC <500/μL [1]. This classification helps to predict the risk of pyogenic infection: only patients with severe neutropenia have significantly increased susceptibility to life-threatening infections. Indeed, ANC of 1.0-1.5 $\times 10^9$/L does not impair host defense; ANC of 0.5-1.0 $\times 10^9$/L may slightly increase the risk of infections [2]. Transient neutropenia is most commonly associated with viral infections [3]. Measles-mumps-rubella vaccine (MMR) administration suppresses polymorphonuclear neutrophils functions without clinical consequences [4]. On rare

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occasions, vaccines containing measles, mumps and rubella antigens can cause thrombocytopenia. As well as after natural measles infection, Immune Thrombocytopenic Purpura (ITP) can also occur after MMR vaccination [4]. However, it is usually not life threating. The risk of thrombocytopenia following MMR vaccination is 1 in 30,000 to 1 in 40,000 vaccinated children [5-9]. The normal platelet count is 150-450 × 10^9/L (150,000-450,000/mm^3). Thombocytopenia refers to a reduction in platelet count to <150/10^9/L (<150,000/mm^3). Okazaki et al. [10], have detected anti-measles and anti-rubella virus IgG antibodies in platelets isolated from a 15-month old child who developed ITP after the sequential administration of measles-rubella, varicella, and mumps vaccines every 4 weeks. This is the first report that shows a direct evidence of thrombocytopenic purpura vaccine-induced.

I conducted a research on PubMed (keyword: transient neutropenia after MMR vaccine) and I did not find any documents. By doing other researches, I found a case published by Markova et al. [11]. Thus, these are the first two cases reported of transient neutropenia after vaccine MMRV.

Markova et al. [11], reported one clinical case of a 13 months old girl, who developed a post vaccination measles infection after a MMR vaccine, followed by a severe neutropenia. The hematological changes lasted more than one year and resolved spontaneously.

Regarding the two cases presented here, in the first of them, transient neutropenia occurred 13 days after the injection of the vaccine, and the neutrophil count returned to normal value 26 days after vaccination. In the second one, neutrophil count reached its minimum on the 9th day after vaccination. Thombocytopenia began on the 8th day after vaccination (98,000) and the count of white blood cells had almost halved compared to the previous value. Seventeen days after the vaccination, neutropenia had not normalized yet. On the 46th day following the vaccine administration the lowest level of platelets was detected (46,000), and neutrophil count returned to normal value.

The availability of blood cells is sustained by pluripotent hematopoietic progenitors. These hematopoietic stem cells (HSCs), which have in common the expression of CD34 surface molecules, are pluripotent cells located in the bone marrow with the ability to differentiate into erythrocytes, granulocytes, monocytes, megacaryocytes and lymphocytes. A variety of viruses have important clinical effects on the hematopoietic system. Hematopoiesis may be inhibited by infection of stem cells, progenitor cells, and the stromal support. The marrow microenvironment is a complex system characterized by many cell types that interact to provide growth factors and other signals to HSCs. Stromal targeting may be a common mechanism used by immunosuppressive viruses to induce hematopoietic suppression [12].

Thrombocytopenia may be caused by an auto-immune reaction, due to infection of megakaryocytes or progenitors, or result from peripheral consumption [13].

Measles virus (MV) disrupts hematopoiesis by infecting human $CD34^+$ cells and human bone marrow stroma. MV infection does not affect the hematopoietic capability of HSCs directly, however, the infection impairs the ability of stroma to support development of HSCs [14]. CD46 has been identified as a cellular receptor for vaccine strains of MV. CD46 is expressed on all nucleated human cells including $CD34^+$ cells. However, antibodies against CD46 could not efficiently inhibit MV infection of HSCs. Wild-type isolates of MV additionally utilize signaling lymphocyte activation molecule (SLAM), for entry. However, SLAM is not expressed on early hematopoietic cells. These results strongly suggest that MV utilizes neither CD46 nor SLAM to gain entry into $CD34^+$ cells, suggesting the presence of an alternative, as yet unidentified third receptor. In contrast, stromal cells appear to be infected via the CD46 receptor, with SLAM possibly functioning as a coreceptor [14].

Therefore, the hypothesis that thrombocytopenia and neutropenia, presented in the second patient on the 8th and 9th day after the vaccine injection, maybe due to a bone marrow effect of the measles vaccine virus on stromal cells, becomes realistic. Alternatively, an effect on the common myeloid progenitor would explain both thrombocytopenia and neutropenia occurring at the same time. Conversely, thrombocytopenia on the 46th day after vaccination may be due to the presence of anti-measles and anti-rubella virus IgG antibodies that can bind to platelets.

These two cases of moderate neutropenia have not led to bacterial infections. Since vaccination is not equivalent to immunization, vaccine injection has not been followed by complete immunization. In fact, a case has not been immunized against Rubella, and the other has not been immunized against Mumps.

Conclusion

Post-vaccination neutropenia is common [15], and the clinical course of these cases is usually transient and benign. In this study there are two children who developed a transient neutropenia related to Priorix Tetra vaccine injection (MMRV). The one of them, also had symptoms very similar to a wild type of measles virus infection, and thombocytopenia. The possibility of hematologic adverse events following MMRV vaccination is real, and not always the vaccinated child is immunized against all the viruses present in this vaccine. In fact, a case has not been immunized against Rosolia, and the other has not been immunized against Mumps. This partial immunization, if presented throughout the population, suggests that immunity control is more important than the mere number of injected vaccine doses.

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