Case report

Recurrent immune thrombocytopenia following different vaccines

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Accepted 5 September 2019

SUMMARY

A boy developed immune thrombocytopenia 2 weeks after receiving his measles-mumps-rubella and varicella vaccines at 12 months of age. He then had a recurrent episode 1 week after the booster doses of his quadrivalent diphtheria-tetanus-pertussis-polio, pneumococcal and meningococcal group C vaccines at 5 years of age. On both the occasions he required hospitalisation and treatment with intravenous immunoglobulin. He received other vaccines, before and in between, without any adverse events. Future vaccines are to be determined on an individual risk-benefit basis and he will be reviewed at the age of 11 when his next routine immunisations are due.

BACKGROUND

Measles-mumps-rubella (MMR) vaccine has been associated with increased risk of immune thrombocytopenia (ITP). There have been case reports and surveillance data suggesting that other vaccines may be possible triggers for ITP, although causality has not yet been established. To the best of our knowledge, this is the first case describing recurrent ITP in a single patient associated with different vaccines.

CASE PRESENTATION

A 6-year-old boy of South Asian descent was referred to the paediatric infectious disease clinic for recurrent immune thrombocytopenia (ITP) temporally associated with immunisation. Two weeks after receiving his 12-month MMR and varicella vaccines, he developed a petechial rash and bruising on his arms and torso. He presented to the emergency department 16 days after vaccination and was found to have isolated thrombocytopenia. He did not have any preceding infectious illness.

He had previously received the hexavalent diphtheria-tetanus-pertussis-hepatitis B-polio-*Haemophilus influenzae* type b, 13-valent pneumococcal and meningococcal MenC conjugate vaccines at 2 months of age, repeat hexavalent and pneumococcal vaccines at 4 months and then his third hexavalent vaccine at 6 months as per the routine infant immunisation schedule with no complications.

He was otherwise healthy and normally developed for his age. His parents and older sister were also healthy, and there was no family history of haematological disorders.

INVESTIGATIONS

When the patient presented to the emergency department his platelet count was extremely low at $8 \times 10^9/L$. On admission, his platelets were $5 \times 10^9/L$ but he had a normal white cell count ($12.7 \times 10^9/L$) and haemoglobin (121 g/L), confirming isolated thrombocytopenia.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for thrombocytopenia in children is broad and can be divided into decreased production, increased destruction and sequestration. Impaired platelet production can be secondary to infection with bone marrow suppression, bone marrow failure or infiltration, nutritional deficiencies and genetic disorders of thrombopoiesis. Platelet destruction can be due to autoimmune processes, such as ITP or drug-induced thrombocytopenia or non-immune processes, such as haemolytic uremic syndrome or disseminated intravascular coagulation. Pooling and sequestration of platelets can occur in patients with hypersplenism or certain types of Von Willebrand disease. Differentiating the causes of thrombocytopenia involves assessment of other cell lines, peripheral blood smears and the overall clinical presentation. In our patient with an acute onset of isolated thrombocytopenia, lack of systemic symptoms and suspected triggers, ITP was felt to be the most likely diagnosis.

TREATMENT

While admitted to the hospital, he received a single dose of intravenous immunoglobulin (IVIG) and his thrombocytopenia resolved within ten days.

OUTCOME AND FOLLOW-UP

Following his episode of ITP, he did not receive the pentavalent diphtheria-tetanus-pertussis-polio-Hib vaccine at 18 months of age, but did receive hepatitis A vaccine at 2 years of age prior to foreign travel.

At 5 years of age, his antibody levels against measles, mumps and rubella were assessed and indicated protective immunity (measles 344 mIU/ml, mumps 832 RU/ml and rubella 66.8 IU/ml) and he had a positive varicella IgG. His platelet count was also normal at this time. Given his protective levels and in line with the WHO recommendations, he was not given his second dose of the MMR vaccine as this was considered to be the most likely cause of the previous ITP episode. However, he did receive the quadrivalent diphtheria-tetanus-pertussis-polio

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To cite: Morin E, Sadarangani M. *BMJ Case Rep* 2019;**12**:e231260. doi:10.1136/bcr-2019-231260

(Tdap-IPV) vaccine, along with pneumococcal and MenC booster doses. One week after these immunisations, he developed bruising on his torso followed by a petechial rash. Again, he had no history of any infectious symptoms. Eight days after the vaccinations, he was seen in the emergency department and again had thrombocytopenia, with all other cell lines within normal limits. On his repeat admission, his platelet count was $<5 \times 10^9/L$. His white blood cell count ($10 \times 10^9/L$) and haemoglobin (120 g/L) were again within normal limits. He was admitted for an infusion of IVIG (1 g/kg), with improvement in his platelet count to $32 \times 10^9/L$ by the following day. He did not have any repeat investigations during the admission due to anxiety relating to blood draws; however, given his rapid improvement in platelet count and his lack of further active bleeding, he was discharged home.

After the second episode of ITP, it was advised that future vaccines be determined on individual risk-benefit basis. We suggested that he be reviewed at age 11 years when his next routine immunisations would be due.

DISCUSSION

ITP is an immune-mediated disease, characterised by an isolated platelet count of $<100 \times 10^9/L$.¹ ITP can be categorised based on the duration of thrombocytopenia: 1) newly diagnosed ITP which resolves within 3 months, 2) persistent ITP lasting for 3 to 12 months or 3) chronic ITP with thrombocytopenia for over 12 months.¹ An infectious illness, most commonly an upper respiratory tract illness, precedes it in around two thirds of new paediatric ITP cases.² Vaccine-preventable infections such as rubella and varicella have also been implicated as triggers for ITP.² Other infections are sometimes identified as causes of secondary ITP, such as hepatitis C virus and HIV.²

The relationship between thrombocytopenia and viral infection is well established and thrombocytopenia may occur during the acute, viremic phase of infection or develop days to weeks after the illness.² There are several postulated mechanisms for thrombocytopenia in the context of viral illness. Antibody-mediated processes have been most commonly implicated, with mechanisms including auto antibody formation against platelet antigens, viral antibodies cross-reacting with platelet surface molecules, viral antigen expression on platelet surfaces and their subsequent targeting, and virus-associated immune complexes binding to platelets resulting in their clearance.^{2,3} Other proposed mechanisms include T-cell mediated cytotoxicity, complement activation and decreased production by megakaryocytes.^{2,3}

The above case is the first report of recurrent ITP following administration of different vaccines. Recurrent ITP is a form of compensated ITP that occurs in an estimated 5% of patients with chronic ITP. During episodes of remission, platelet destruction is balanced by increased production by the bone marrow. With triggers that result in marrow suppression (such as infection), exacerbations may occur, with recurrence of thrombocytopenia and associated symptomatology.⁴

As vaccines mimic infection to produce immunological protection, it is plausible that they could be associated with ITP. In fact, the association of the live-attenuated MMR vaccine with ITP is well-described with a causal relationship affirmed in the 1994 Institutes of Medicine report.⁵ There are several possible mechanisms to explain the pathogenesis of vaccine-associated ITP, the most likely being molecular mimicry, where epitopes in vaccine antigens, or even adjuvants in the vaccine, cross-react with self-peptides. This results in activation and proliferation of B-cells and the production of auto-antibodies. These antibodies

act on the platelets but may also act on the megakaryocytes to inhibit or destroy platelet precursors. The increased level of certain cytokines during active ITP, such as the B lymphocyte stimulating factor, also support the role of an uncontrolled B-cell response. After being bound by auto-antibodies, platelets and megakaryocytes can be destroyed by opsonisation, complement activation or apoptosis. In cases where antiplatelet antibodies are not detected, the mechanism of ITP is thought to be due to T-cell dysregulation and cytotoxicity and increased production of proinflammatory cytokines and chemokines, such as interferon-gamma (IFN- γ), tumour necrosis factor (TNF) and C-X-C motif chemokine 10 (CXCL10).⁶ The association between the MMR-vaccine and ITP is well supported and the presence of platelet-binding anti-measles and anti-rubella IgG antibodies has been noted in children with ITP following vaccination against measles, rubella, mumps and varicella.⁷ However, the relationship between ITP and other vaccines is less well-defined.

Our patient's first episode of ITP occurred following his first dose of the live attenuated MMR vaccine. The incidence of MMR vaccine-associated ITP is between 1 in 25 000 to 1 in 40 000 doses of MMR^{2,3} compared with an incidence of about 1 in 3000 following measles infection.⁸ There is evidence that the natural history of MMR vaccine-associated ITP is more self-limited than other forms of ITP, with shorter durations of admission and higher platelet counts.⁸ Children with a history of ITP prior to the first dose of MMR are not at risk of vaccine-associated ITP⁹ and, in children with no history of ITP with the first MMR vaccine, there does not seem to be an increased risk of ITP associated with the second dose.¹⁰ There are rare reports of recurrent MMR vaccine-associated ITP;¹¹ however, several studies assessing outcomes of children with one episode of MMR-associated ITP who received a second MMR dose found no recurrence with subsequent vaccination.^{9,12,13} Despite this, current recommendations are that patients with a history of MMR vaccine-associated ITP should not receive their second dose if they have protective antibodies on serological testing,¹⁰ as in this case.

The association between ITP and other vaccinations is unclear. Case reports and surveillance data have implicated diphtheria, tetanus and pertussis (DTP)-containing vaccines and the hepatitis B vaccine;^{14–16} however, the Institutes of Medicine report does not support causal links for vaccinations other than MMR.⁵ One study examined a retrospective cohort of 1.8 million children and found no increased risk of ITP with vaccinations other than MMR below the age of 19 months.¹⁷ In older age groups, the risk was reported to be increased following varicella, DTP and hepatitis A vaccines; however, these associations could not be considered as conclusive evidence of causality because of the rare occurrence rates. A study based on the Canadian Immunisation Monitoring Programme, ACTIVE surveillance system reported 107 cases of vaccine-associated ITP, 30 of which were linked to non-MMR vaccines. However, 71% of the cases had symptoms of preceding viral illness which may have been an alternative cause of the documented thrombocytopenia.¹³ In a report from the US Vaccine Adverse Events Reporting System (spanning 18 years (1990–2008), there were 478 cases of MMR vaccine-associated ITP; however, there were 962 reports of thrombocytopenia following non-MMR vaccinations. Of the cases reported with single vaccine use, the most commonly associated non-MMR vaccine was hepatitis B, with 226 cases, while each of the other cases had under 50 cases documented.¹⁶ More specifically, there were only 47 cases associated with varicella vaccine, 32 with hepatitis A vaccine and eight with DTP vaccine.¹⁶

The possibility of recurrent ITP associated with vaccines other than MMR is even less well-described. There is one case report in literature describing recurrent ITP associated with repeated influenza vaccination.¹⁸ In our case, the patient had an initial episode of MMR vaccine-associated ITP followed by an episode of ITP after being immunised with vaccines other than MMR, although it is impossible to determine which of the Tdap-IPV, pneumococcal and meningococcal vaccines was the trigger.

Recurrent ITP, as a form of chronic ITP, is uncommon and the natural history of the disease is hard to predict but, as exacerbations may have different triggers, it is possible that this child may develop further episodes in the future. Furthermore, given that there are no other cases of ITP triggered by different vaccines in the same patient and the lack of definitive epidemiological associations between ITP and non-MMR vaccines, it is difficult to provide recommendations regarding continuing the vaccination series in this patient. Nonetheless, this case demonstrates that, while uncommon, it is possible for patients to have multiple episodes of ITP triggered by different vaccines and that this should be considered in individuals with recurrent ITP temporally associated with their immunisation schedule.

Learning points

- ▶ Immune thrombocytopenia (ITP) is an uncommon adverse event post-vaccination, with causality established only with the MMR vaccine.
- ▶ This case demonstrates that it is possible to develop recurrent ITP following different vaccines.
- ▶ Decisions regarding future immunisations in children with recurrent vaccine-associated ITP have to be made on an individualised basis given the rarity of this occurrence.

Contributors Both authors conceived the idea for the manuscript. MS was responsible for care of the patient. Both authors collected data for the manuscript. EM wrote the first draft of the manuscript. Both authors critically reviewed the manuscript and approved the final version for submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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