Recurrent Immune Thrombocytopenia After Influenza Vaccination: A Case Report

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Immune thrombocytopenia (ITP) is an isolated autoimmune condition, often preceded by a viral infection. Vaccines, mainly the measles-mumps-rubella vaccine, have also been associated with an increased risk of developing the disease. Although some case reports of ITP after influenza immunization in adults have been published, epidemiologic studies examining the role of the influenza vaccine as a trigger of ITP have not conclusively proven causality. We report a child with 3 occurrences of ITP, each within 1 week of receiving the influenza trivalent inactivated vaccine. He recovered fully in-between the episodes, and no further episodes have occurred since discontinuation of seasonal influenza vaccination. To the best of our knowledge, this report is the first showing, with high probability, the influenza vaccine as a cause for ITP in a pediatric patient.

Immune thrombocytopenia (ITP) of childhood (previously known as idiopathic thrombocytopenic purpura) is characterized by isolated, immune-mediated thrombocytopenia (blood platelet count <100 000/μL) with an otherwise normal blood cell count.[1] Almost all patients diagnosed with ITP have signs of cutaneous bleeding (petechiae, purpura, and ecchymoses). Mucosal bleeding can occur in as many as 40% of children, usually involving the nasal passages and buccal and gingival surfaces. Less often, the gastrointestinal and genitourinary tracts are affected. Serious bleeding occurs in ∼3% of children with ITP. The most feared manifestation, intracranial hemorrhage, may develop in ∼0.5%.

The majority of pediatric ITP cases resolve within 3 months. Some children will have the persistent form of ITP, defined by failure to achieve spontaneous remission or to maintain remission without treatment, lasting between 3 and 12 months. Approximately 20% of children[2,3] and the majority of adults develop chronic ITP, defined by ITP lasting ≥12 months.[1]

In ∼60% of cases, there is a history of an earlier infection within the past month, but a specific pathogenic trigger is only rarely discovered. A very small increased risk of developing ITP in the 6 weeks after a measles-mumps-rubella (MMR) vaccination has been shown. To the best of our knowledge, influenza vaccination has not convincingly been shown to trigger ITP to date.

CASE REPORT

A 4.5-year-old boy of Sephardic Jewish origin presented to our medical center in October 2013 with cutaneous and mucosal bleeding. Blood counts and confirmatory blood smear revealed a decreased platelet count of 17 000/μL, with normal hemoglobin levels and white blood cell counts (Supplemental Table 1). Results of the

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chemistry profile and routine blood coagulation tests were normal, and no acute infection was reported in the preceding weeks. He was treated with a single dose of intravenous immunoglobulin (IVIG), and his platelet levels returned to normal within 10 days.

On review of the patient's medical history, it became apparent that he had been hospitalized twice previously, at 1.5 and 3.5 years of age, with similar signs and symptoms. In November 2010 (age 1.5 years), he presented with cutaneous and mucosal bleeding, after 4 days of fever and an upper respiratory tract infection. Blood cell counts demonstrated thrombocytopenia 3000/μL, with a confirmatory blood smear and normal chemistry panel. He was treated with 2 courses of IVIG followed by a course of prednisone 4 mg/kg/d for 4 days, with a rise in the platelet count to 49 000/μL. He had complete resolution of the thrombocytopenia within 2 months, with normal blood cell counts during routine follow-up over the next 2 years.

In November 2012 (age 3.5 years), the patient was again admitted due to cutaneous and mucosal bleeding, as well as subconjunctival hemorrhaging. Blood cell counts demonstrated thrombocytopenia of 2000/μL, with no other abnormalities. No preceding acute infection was reported. He was treated with a course of IVIG. Due to a partial response and clinical symptoms of aseptic meningitis attributed to the IVIG treatment, the child was further treated with oral prednisone and later with pulse methylprednisolone therapy, with complete resolution of the thrombocytopenia within 2 months. Normal blood cell counts were observed for 10 months until the third episode of thrombocytopenia at age 4.5 years.

The child is normally developed for his age, with normal growth on the 10th percentile of weight and 50th percentile of height. He has a history of recurrent wheezing and recurrent episodes of otitis media, in addition to an admission at 1 year of age for pneumococcal bacteremia. His vaccinations, including the pneumococcal vaccine, are up-to-date according to the recommended schedule of the Israeli Ministry of Health, with no known allergies to food or drugs.

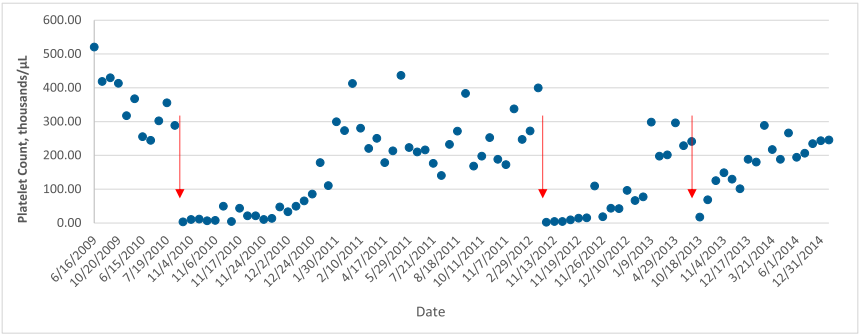

FIGURE 1
A chart displaying platelet count according to dates. Trivalent influenza vaccine immunization dates are marked by a red arrow.

During the child's most recent admission, he was evaluated for possible immunodeficiencies; immunoglobulin levels were within normal range, the direct antiglobulin test result was negative, lymphocyte subset panel (including CD8, CD4-, and CD3+) were within normal range, and lupus anticoagulant, β_2-glycoprotein 1 antibodies, and anticardiolipin antibodies were negative. Results of antinuclear antibody and HIV testing were negative. Specific antibodies to diphtheria and tetanus were within normal levels.

During a review of the patient's medical records, it was noticed that all 3 admissions for ITP occurred within 1 week of immunization with the trivalent inactivated influenza vaccine. Symptoms appeared within 7 days of the first vaccination at age 1.5 years and within 6 days of the second and third vaccinations at age 3.5 years and 4.5 years, respectively. During the fall of 2011 (age 2.5 years), he did not receive the annual influenza immunization, and indeed no symptoms of ITP appeared (Fig 1). In all 3 cases, the child was immunized with the Fluarix trivalent influenza vaccine (manufactured by GlaxoSmithKline Biologicals, Dresden, Germany). The strains included in the immunization are available in Supplemental Table 2.

After the most recent recurrence of ITP, it was advised that the child discontinue annual influenza vaccinations. The patient is currently 7 years old, and no further recurrences have been documented. At close follow-up, the platelet count has remained within normal range (Supplemental Table 1). Using the World Health Organization–The Uppsala Monitoring Centre system for standardized case causality assessment, we found that our case fell under the "certain" causality category (Fig 2).

DISCUSSION

The annual incidence of ITP is estimated at 1 to 6 per 100 000 children.[5] Recurrent ITP, defined as the recurrence of ITP after at least 3 months of remission sustained without treatment, is estimated to occur in ~4% of all children with ITP; it is more common in female subjects and can occur after an acute or chronic course of ITP.[6] A second recurrence in the pediatric age group

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary

FIGURE 2
World Health Organization–The Uppsala Monitoring Centre "certain" causality category criteria.[4]

seems to be fairly rare, with only a few reports available in the English medical literature. In 1 such study among 340 children with ITP and up to 4 years of follow-up, 14 (4.1%) had a first recurrence, but only 1 patient (0.29%) had a second recurrence. Another retrospective study showed a second recurrence rate of 1.8%, but it included cases reoccurring <3 months apart.[7]

The cause of ITP remains unknown in most cases, but it can be triggered by a viral infection or other immune triggers, such as vaccination, most likely by the mechanism of molecular mimicry but possibly by other constituents of the vaccine.[8] The formed autoantibodies are directed against platelet membrane antigens. The antibody-coated platelets are rapidly cleared by tissue macrophages, resulting in a shortened half-life. In addition, the antibodies may also inhibit platelet production.

In a large systemic review, the risk of developing ITP in children and adolescents after vaccination was not increased for any of the vaccines other than the MMR.[9] The MMR is the only vaccine widely considered to have demonstrated a cause-and-effect relationship,[10] with 1 to 3 additional children developing ITP for every 100 000 vaccine doses given.[11] Individual case reports have described a possible association of ITP with other vaccines such as the varicella, tetanus-diphtheria-acellular pertussis, poliomyelitis, pneumococcal, hepatitis A and hepatitis B, rabies, and human papillomavirus vaccines.[8]

In a retrospective data review by Moulis et al,[12] the influenza vaccine was deemed a possible cause of ITP, although the investigators were unable to calculate the risk for ITP after influenza vaccination; conversely, a case–control study by Garbe et al[13] concluded that the influenza vaccine was a probable cause of ITP according to the World Health Organization standardized causality assessment,[4] with an odds ratio of 3.8 (95% confidence interval 1.5–9.1). In addition, some individual reports of ITP occurring in adults within 4 to 17 days after influenza vaccination have been published.[14–20] To date, there has been only 1 reported case of ITP in the pediatric population, occurring 26 days after vaccination of a second dose of the influenza vaccine. In that particular case, the investigators concluded that there is insufficient evidence to indicate a causal relationship between the influenza vaccine and symptomatic thrombocytopenia.[21] In Israel, ~1.5 million people (18% of the population) were vaccinated yearly in the relevant period, with similar vaccine uptake (19%) in children aged <5 years (Annual Influenza Vaccine Reports, 2010-2014, Israeli Ministry of Health [not available in the public domain]). Querying the pharmacovigilance program of the Israeli Ministry of Health, a voluntary consumer and provider reporting program, we were unable to detect any other case of ITP attributed to the influenza vaccine. To the best of our knowledge, no cases of thrombocytopenia were reported in the vaccine's preapproval or postapproval periods.

Natural influenza infection is rarely associated with immune hematologic disorders.[22] However, it is known to induce cytopenias,[23] and thrombocytopenia is a known complication of acute influenza infection.[24] Although the incidence of thrombocytopenia after a confirmed infection is unknown, it was found to occur in up to 14% of patients hospitalized with 2009 H1N1 influenza in the United States.[25] Thrombocytopenia was also common in children requiring hospitalization for confirmed avian influenza H5N1 in Thailand in 2004, occurring in 4 (44%) of 9 children.[26]

CONCLUSIONS

We report the case of a child with 3 occurrences of ITP, each preceded by an influenza vaccination 6 to 7 days before the onset of symptoms. This report is therefore the first to show with a high degree of confidence an association between the trivalent influenza vaccine and the development of ITP. The response to IVIG therapy strongly suggests an immunologic mechanism rather than a cytotoxic one.

When assessing a patient with ITP, it is important for the clinician to inquire about recent infections, medications, and vaccinations, as the occurrence of ITP in association with a certain medication or vaccination might affect the clinicians' decision to treat or re-immunize with the offending agent.[27] It is important to take into account that the attributable risk of the influenza vaccine as a cause for ITP is clearly low, due to the high prevalence of influenza vaccination and rarity of reports. Because the safety profile of the vaccine has been shown to be favorable, and the benefits of disease prevention

are high, this case should not alter the recommendations to immunize patients with the influenza vaccine. Furthermore, it is clear that the risk of developing thrombocytopenia is much higher after being infected with influenza than after receiving the immunization. Nevertheless, we wish to alert the clinician to this possible adverse effect of the vaccine, underscoring the importance of careful history-taking in patients with recurrent ITP.

ABBREVIATIONS

ITP: immune thrombocytopenia
IVIG: intravenous immunoglobulin
MMR: measles-mumps-rubella

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