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FRONTIERS IN AUTOIMMUNITY

Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases

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Abstract Immune thrombocytopenic purpura (ITP) is an autoimmune condition characterized by low platelet count with mucocutaneous and other bleedings. Clinical manifestations may range from spontaneous formation of purpura and petechiae, especially on the extremities, to epistaxis, bleeding at the gums or menorrhagia, any of which occur usually if the platelet count is below 20,000 per μl. A very low count may result in the spontaneous formation of hematomas in the mouth or on other mucous membranes. Fatal complications, including subarachnoid or intracerebral, lower gastrointestinal or other internal bleeding can arise due to an extremely low count. Vaccines may induce ITP by several mechanisms. Vaccine-associated autoimmunity may stem not only from the antigen-mediated responses but also from other constituents of the vaccine, such as yeast proteins, adjuvants, and preservatives diluents. The most likely is through virally induced molecular mimicry. The binding of pathogenic autoantibodies to platelet and megakaryocytes may cause thrombocytopenia by different mechanisms, such as opsonization, direct activation of complement, or apoptotic pathways. The autoantibodies hypothesis is not sufficient to explain all ITP cases: In the anti-platelet antibody-negative cases, a complementary mechanism based on T cell immune-mediated mechanism has been suggested. In particular, T cell subsets seem dysregulated with an increased production of pro-inflammatory cytokines, as IFN-γ and TNF, and chemokines, as CXCL10. Vaccines are one of the most striking discoveries in human history that changed dramatically life expectancy. Nonetheless, the occurrence of adverse events and autoimmune phenomena has been described following vaccination, and ITP may represent one of this.

Keywords Immune thrombocytopenic purpura · Infections · Vaccines · Autoimmune diseases · ASIA · Influenza · Autoantibodies

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Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune condition characterized by low platelet count with mucocutaneous and other bleedings. Clinical manifestations may range from spontaneous formation of purpura and petechiae, especially on the extremities, to epistaxis, bleeding at the gums or menorrhagia, any of which occur usually if the platelet count is below 20,000 per μl [1]. A very low count (<10,000 per μl) may result in the spontaneous formation of hematomas in the mouth or on other mucous membranes. Fatal complications, including subarachnoid or intracerebral, lower gastrointestinal or other internal bleeding can arise due to an extremely low count (<5,000 per μl).

The pathogenesis of ITP entails antibody-coated platelets, which may undergo reticuloendothelial phagocytosis resulting in a reduced platelet survival [2, 3]. Despite the evidence for autoantibodies against several platelet surface glycoproteins (GP), the anti-glycoprotein IIb/IIIa being the most important, the spark is not yet recognized. It has been proposed that an uncontrolled immune response may enable cytokine pro-inflammatory milieu on the base of a genetic susceptibility background [4–6]. Thus, the trigger of these autoimmune phenomena may be searched within infectious agents, and the suggested mechanism may be molecular mimicry. There are evidences suggesting as Helicobacter pylori CagA protein may act through molecular mimicry in the pathogenesis of Helicobacter pylori-associated chronic idiopathic thrombocytopenic purpura [7]. Moreover, the eradication of such infection can lead to an increased platelet count in patients with ITP [8]. Indeed, more than 20 % of pediatric patients with ITP had a preceding viral infection, and the incidence of ITP following measles or rubella infections was estimated at 1:6,000 for measles and 1:3,000 for rubella [9–11].

Nonetheless, it is not surprising that ITP may develop subsequently after vaccination [12, 13], and in this review, we will focus on this aspect of ITP pathogenesis.

ITP pathogenesis

Vaccines may induce ITP by several mechanisms. Vaccine-associated autoimmunity may stem not only from the antigen-mediated responses but also from other constituents of the vaccine, such as yeast proteins, adjuvants, and preservatives diluents. The most likely is through virally induced molecular mimicry. Antibodies responsible for the clearance of virus antigens may cross-react with antigens naturally present on platelets. These autoantibodies are mainly IgM directed toward platelet surface antigens and transiently detected in a majority of the children with acute ITP.

The self-limiting nature of acute ITP has been explained by the sudden disappearance of IgM antibodies. The influenza virus *per se* has a direct effect on platelets. An H3N2 virus added directly to platelets was found to induce clumping of both human and rabbit platelets. Thus, the infusion of influenza virus into rabbits induced rapid thrombocytopenia. In humans, an increased formation of platelet–monocyte aggregates and increased binding of the PAC-1 antibody have been described, leading to the binding of the active conformation of $\alpha_{IIb}\beta_3$ integrin on platelets [14, 15]. Moreover, it can be speculated that especially in infants, in whom the idiotypic network is still developing, there is a higher likelihood of cross-reactive autoantibody expression after infections and vaccinations.

Vaccines, as well as infections, activate immune-mediated mechanisms that can induce protective immunity. Because vaccines induce an immune response that mimics natural infection to produce immunologic protection, it is theoretically possible that all the vaccines could trigger the development of ITP. Currently, the pathogenic mechanisms of ITP have not been fully elucidated. As for all the autoimmune conditions, the presence of a trigger in a genetically predisposed individual could determine the development of an uncontrolled immune response. Both the acquired and innate immunity could be involved in ITP pathogenesis.

The molecular mimicry is considered the classic pathogenetic pathogenic mechanism responsible for ITP development after vaccinations. The epitope, integrated within the vaccine antigen, shares a similar structure with a self-peptide, driving toward self-reactivity. The consequent polyclonal activation and the proliferation of B cells cause the autoantibodies production. Notably, the antigen-mediated responses could be induced not only by the infective components of the vaccine, but also from other constituents, such as adjuvants [16]. The central role of B cells was demonstrated by the identification of an increased number of this cellular type in the spleen section of ITP patients [17].

The autoantibodies produced through this mechanism, generally IgG, interact with several platelet surface GP. The surface molecules, organized as heterodimers, act as receptors by mediating two important functions, namely the adhesion to the sub-endothelial matrix and platelets aggregation [18]. The GPIIb-IIIa and/or GPIb-IX autoantigens were identified as the most likely ligands for anti-platelet autoantibodies in ITP. Moreover, autoantibodies against GPIa-IIa and GPIV were also identified by antigen-capture techniques. These antibodies represent the hallmark of the disease, with a sensitivity of 49–66 % and a specificity of 78–93 % [19].

Okazaki et al. [20] identified the direct interplay between the vaccination and the development of anti-platelets antibodies. These authors demonstrated the production of platelet-binding anti-measles and anti-rubella virus IgG antibodies in a 15-month-old infant presented with ITP after sequential administration of measles/rubella combined vaccine, varicella vaccine, and mumps vaccine every 4 weeks.

The presence of increased levels of B lymphocyte stimulator (BLyS) has been recently identified in active ITP patients, suggesting its participation in the uncontrolled B cells proliferation and survival [21]. Moreover, similarly, in patients affected by systemic lupus erythematosus (SLE), Emmerich et al. [21] identified an association between ITP and the polymorphism −871 in the promoter region of gene codifying for BLyS, associated with higher protein levels.

As widely demonstrated, BLyS plays a crucial role in the B cells development, survival and antibody production: The increased expression of BLyS results in the escape of self-reactive B cells from the anergy, with the development of autoimmune phenomena [22].

As above mentioned, the innate immunity could play a role in ITP pathogenesis. In particular, dendritic cells (DCs) could be an important player in ITP pathogenesis, due their increased ability to present apoptotic platelets to T lymphocytes [23]. Growing evidences have recently suggested that activated DCs could directly contribute to B cell hyperactivity by inducing their proliferation and increased antibody production. This effect seems related to the ability of DCs to release BLyS, as demonstrated by the increased of the expression of this survival factor on DCs in patients with ITP [24]. Moreover, the authors demonstrated that the stimulation of DCs with R848, known as Toll-like receptor 7 (TLR7) ligand, could induce the production of vast amounts of BLyS, favoring the production of the anti-platelet antibodies production in in vitro culture systems [24]. Taken together, these results suggest the role of a new TLR7/BAFF/BAFF-R pathway involved in ITP pathogenesis [22]. The autoantibodies detected in ITP patients could operate not only on the platelet, but also on megakaryocyte by inducing, both in vitro and in vivo, the inhibition and/or the destruction of platelet precursors [25, 26].

The binding of pathogenic autoantibodies to platelet and megakaryocytes may cause thrombocytopenia by different mechanisms, such as opsonization, direct activation of complement, or apoptotic pathways [22]. The spleen is the major site of clearance of antibody-coated platelets in ITP. Concerning the role of the complement, the consumption of the plasma components and their deposition on platelets have been demonstrated in ITP, suggesting that such deposition could contribute to platelet clearance [22].

The autoantibodies hypothesis is not sufficient to explain all ITP cases: In the anti-platelet-antibody-negative cases, a complementary mechanism based on T cell immune-mediated mechanism has been suggested. In particular, a dysregulation of T cell subsets was described, with a prevalence of Th1 profile and an increased production of pro-inflammatory cytokines, as IFN-γ and TNF, and chemokines, as CXCL10 [27–29].

More recently, the role of other T cell subsets, such as Th-17 and T-reg, was suggested. First, Zhang et al. [30] in 2009 described a significantly higher percentage of Th17 in ITP patients, with a positive correlation with Th1. Furthermore, increased serum levels of IL-17A, the major pro-inflammatory cytokine produced by Th17 cells, and of the cytokines involved in the Th17 cell activation and maintenance, such as IL-1b, IL-6 and IL-23, were identified in ITP patients [31]. Cao et al. [32] confirmed these findings by describing a higher percentage of Th17 cells especially during active disease. Conversely, the percentage of Treg cells was significantly decreased, suggesting that the imbalance of Th17/Treg ratio could play a critical role in ITP pathogenesis. Alternatively, functional defects in Treg cells were described in ITP [29]. Finally, cytotoxic T cells could exert a direct lytic effect on platelets and/or megakaryocytes. CD8 + T cells from patients with active ITP bound to platelets in vitro leading to a direct platelet lysis, while CD8 + T cells from patients in clinical remission did not have a significant platelet reactivity [33].

Figure 1 summarizes the possible pathogenic mechanisms of ITP.

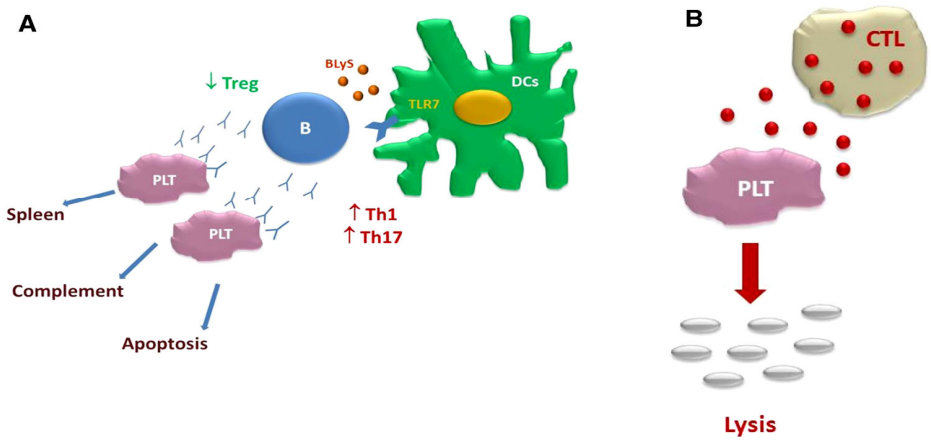

Fig. 1 Pathogenic mechanism of ITP. **a** Autoantibody-mediated platelet destruction; **b** Cytotoxic T cells (CTL)-mediated platelet lysis

ITP and vaccines

Immune thrombocytopenic purpura is a brick in the mosaic of autoimmunity. ITP may be part of a "classic," systemic, autoimmune disease, with 12 % of patients with thrombocytopenia experiencing an evolution into an overlapping autoimmune disease. It has been showed that more than 20 % of pediatric patients with ITP had a preceding viral infection. ITP onset may occur following several vaccinations including measles–mumps–rubella (MMR), hepatitis A and B, diphtheria–tetanus–acellular pertussis (DTaP), and varicella [34]. Although uncommon, ITP may also develop following influenza vaccination. The interplay between vaccines and autoimmunity is very close to the established association between infections and autoimmunity. Infectious agents can cause/trigger autoimmunity through several mechanisms such as molecular mimicry, bystander activation, polyclonal activation, and the presence of super-antigens [35]. Vaccines, as well as infections, may activate immune-mediated mechanisms that can induce protective immunity, but, on the other hand, may lead to an autoimmune response.

ITP and influenza vaccine

In a recent study, Garbe et al. found that influenza vaccine has a "probable" causality to induce ITP [36]. Pneumococcal and poliomyelitis vaccine were also assessed as probably causing ITP. These data were confirmed in the case–control analysis that showed a significantly increased risk (fourfold, adjusted for sex, age and other drugs) for influenza vaccination.

The authors conclude suggesting that a new onset of ITP should not only direct attention to drugs as possible etiological agents, but also to vaccines that are known to cause autoimmune phenomena. In another survey, eight cases of influenza vaccine-induced thrombocytopenia were described [37]. Within the 59 drug-induced ITP, 45.8 % were post-vaccines and mainly occurred in children. Data from the literature suggest also that vaccine-induced ITP is rarely severe. Moreover, the influenza vaccine may trigger and worsen a preexistent thrombocytopenia [38].

A number of other cases have been reported from Greece [39], Japan [40, 41], Israel [13], France [42], China [43], and Italy [44]. Furthermore, it is well known that thrombocytopenia can relapse in patients with ITP after influenza vaccination [45]. Even in the recurrence of ITP, a role for vaccines has been suspected. [46].

In a recent review, the adjuvants contained in the A/H1N1 were less likely to be determinant for the onset of autoimmune manifestations [47]. In this study, 50,221 adverse reactions following vaccination with influenza A/H1N1 were reported to the EudraVigilance; of these, 314 were autoimmune diseases. ITP was reported in 28 cases, and it was the third most common autoimmune disease associated with H1N1 vaccination (after Guillain-Barré syndrome and rheumatoid arthritis).

A recent report on adverse events following pandemic (H1N1) 2009 vaccine in Taiwan found that ITP was spontaneously reported within 0–42 days of vaccination, suggesting a strict time relationship with vaccination [48]. Most patients required treatment with glucocorticoids, and in some cases, the introduction of intravenous immunoglobulin or immunosuppressive treatment was necessary.

In influenza, the target of molecular mimicry probably involves hemagglutinin (HA). This glycoprotein is a major surface protein of the influenza virus. It fosters binding of viruses to cells with sialic acid on their membranes, such as respiratory tract cells or erythrocytes [49]. HA is a primary target of neutralizing antibodies, which act by inhibiting the virus attachment to target cells. HA is the main antigen in influenza vaccines. A high-dose influenza vaccine contained HA of three different influenza virus strains (H1N1, H3N2 and B virus) [50]. It has been demonstrated that HA also binds to platelets, through receptors bearing a terminal N-acetyl neuraminic acid group displayed on their surface. Consequently, the membrane-bound HA can be recognized by the anti-HA antibodies, triggering activation of the complement cascade which induces platelet lysis and thrombocytopenia. In Table 1 are summarized the reports linking influenza vaccination and ITP from the literature.

ITP, poliomyelitis and pneumococcal Vaccines

Furthermore, several case reports of ITP-related to poliomyelitis vaccination have been published [43, 51, 52]. Twelve cases of severe thrombocytopenia (<20,000/μL) were reported for the 7-valent pneumococcal vaccination from the US Vaccine Adverse Event Reporting System; however, with the exception of one case, all subjects had received other vaccinations or drugs [53]. In another study, only one case of ITP was observed in a randomized, modified double-blind trial in 936 adults aged 70 years and older who had previously received PPSV23 at least 5 years before study entry and were now vaccinated with PCV13 or PPSV23 [54].

ITP and hepatitis B virus vaccine

The HBV vaccine has been used routinely for more than 20 years. Autoimmune phenomena, including erythema nodosum, lichen planus, vasculitis, glomerulonephritis, Evan's syndrome, rheumatoid, and reactive arthritis, have

Table 1 Reports linking influenza vaccination and ITP

Note	Other side effects/complications	Patient (s)	Study
No differences in the reporting of autoimmune disorders between adjuvanted and non-adjuvanted A/H1N1 vaccines	314 autoimmune disorders including type 1 diabetes mellitus, multiple sclerosis, Guillain–Barre syndrome, and acute disseminated encephalomyelitis	Of the 50,221 adverse reactions received in EudraVigilance for A/H1N1 vaccines (adjuvanted: 46,173, non-adjuvanted: 4,048), Idiopathic thrombocytopenic purpura	Isai et al. [47]
		28 total, 5 non-adjuvanted (13,2 %), 23 adjuvanted (6 %)	
Full recovery with a single dose of intravenous immunoglobulin in two days	None	Healthy 3-year-old boy	Mantadakis et al. [39]
		ITP onset 26 days after immunization	
Refractory to high-dose immunoglobulin therapy, prednisolone, and splenectomy	None	Healthy 79-year-old man	Tsuji et al. [40]
		Onset with generalized petechiae. ITP onset 4 days after immunization	
Partial recovery with Cyclosporin A administration (PLT count 50,000/microl)		Platelet count at onset: 4,000/microl	
Full recovery with corticosteroids		75-year-old patient with prior autoimmune liver disease	Mamori et al. [41]
		ITP onset 7 days after immunization	
		Platelet count at onset: 5,000/microl	
Full recovery with high-dose intravenous immunoglobulins and pulse intravenous methylprednisolone	None	19-year-old patient with acute lymphoblastic leukemia	Ikegame et al. [82]
		Platelet count at onset: 10,000/mcl.	
		ITP onset 17 days after immunization	
Full recovery with corticosteroid therapy within ten days	Serum antiplatelet antibodies were detected in high titer and bone marrow aspiration revealed an increased number of megakaryocytes	32-year-old healthy patient	Casoli and Tumiati [44]
		onset with petechiae and ecchymoses	
		ITP onset 15 days after immunization	
Full recovery with corticosteroids and IVIg	Gastrointestinal bleeding	68-year-old healthy patient	Tishler et al. [13]
		ITP onset 14 days after immunization. Platelet count at onset: 3,000/mcl	
Full recovery after corticosteroids		38-year-old patient with Chronic obstructive pulmonary disease	Kelton et al. [45]
		ITP onset 14 days after immunization	
		Platelet count at onset: 32,000/mcl	
Full recovery after corticosteroids		72-year-old healthy patient	Granier et al. [42]
		ITP onset 8 days after immunization	
		Platelet count at onset: 3,000/mcl	

been observed subsequently after the administration of the vaccine. Even more frank autoimmune conditions, such as Guillain–Barre syndrome and SLE, have been, though sporadically, described. If thimerosal was first claimed to be responsible for these adverse events, this preservative is not in the vaccine anymore and the adjuvant used, aluminum hydroxide, and other components of the vaccine, such as yeast, were then suspected [55].

Three cases of ITP were described after the first dose of recombinant hepatitis B vaccine in infants under 6 months of age [56]. Interestingly, the authors aimed at excluding all other possible confounders while they found antiplatelet antibodies. These were not the first cases; since in 1994, Poullin and Gabriel reported on two young females who suffered from thrombocytopenia after the second and third dose of HBV vaccination, respectively [57]. In 1995, Meyboom et al. described 28 cases of thrombocytopenia after using hepatitis B vaccine, suggested a possible relation between vaccine and thrombocytopenia in eight of them since general symptoms were present. The thrombocytopenia was reversible, and no anti-hepatitis B gammaglobulin or other suspected drugs were recorded. In most of the cases, the course was mild and corticosteroid treatment was effective [58].

In 1998, recombinant hepatitis B vaccine administered to seven children, mean age of 12 years, was suspected to

be associated with thrombocytopenia and haemorragic manifestions in four of these patients. Infectious and other immune etiologies were excluded in all cases; however, three of them already suffered from thrombocytopenia. Glucocorticoids, high-dose intravenous immunoglobulin, or both were successfully used [59].

Geier and Geier, in a case–control epidemiological study, found an increased risk for thrombocytopenia (OR 2.3, $p < 0.04$, 95 % CI 1.02–6.2) in HBV-vaccinated subjects in comparison with an age-, sex-, and vaccine year-matched unexposed tetanus-containing vaccine (TCV) group [60]. In a recent case from Turkey, a more sever course was observed with a very low number of platelet and the need for a successful usage of intravenous immunoglobulin (IVIG) [61]. In a study performed in Taiwan, 12 out of 20 ITP cases described developed after vaccination and eight were considered idiopathic [62]. In particular, five ITP cases occurred after the second dose of hepatitis B virus vaccine at 1 month of age; four occurred after the first dose of DTaP-containing vaccine at 2–3 months of age; two occurred after the first dose of MMR vaccine at 16 months of age; and one occurred after the first dose of varicella vaccine at 14 months of age. One of these 12 cases, who also had a marked decrease in hemoglobin level without bleeding, was suspected to have Evans' syndrome [62]. However, there are several potential confounding factors involved in such alleged association.

ITP and MMR vaccine

While the incidence of ITP following measles or rubella infections is estimated at 1:6,000 for measles and 1:3,000 for rubella, transient but possibly severe thrombocytopenia occurs with an incidence of 1 in 25,000–40,000 MMR vaccinations [9–11]. An Italian case–control study found a 2.4-fold risk (95 % CI 1.2–4.7) of ITP after MMR vaccine [63]. The most detailed paper on ITP and MMR vaccine is a systematic review published in 2010. The authors found 12 relevant articles suggesting an incidence of such adverse event from 0.087/100,000 in Japan to 4/100,000 MMR doses in UK (median incidence 2.6/100,000 doses). In all instances, details concerning the clinical course of MMR-associated ITP were scarce. The MMR-associated thrombocytopenia seems to be benign in most cases, with resolution within 6 months from diagnosis in 90–95.8 % of the affected children. Miller et al. suggested that MMR-associated ITP was more self-limited compared with the non vaccine-associated ITP. Only 10 % of the cases appear to turn in a chronic form of the disease, while therapy with steroids and/or IVIG is effective in most cases. It was underlined that it is appropriate to delay vaccination during resolution of acute ITP or immunosuppressive treatment.

O'Leary et al. [64] performed a retrospective cohort study on 1.8 million vaccinated children actively enrolled in their respective health plans. The authors described 197 chart-confirmed ITP cases and found that there was an elevated risk of ITP after MMR vaccine in the 12- to 19-month age group. Moreover, there was a significantly elevated risk of ITP after hepatitis A vaccine at 7–17 years of age and for varicella vaccine and tetanus–diphtheria–acellular pertussis vaccine at 11–17 years of age. Most cases were acute and mild with no long-term sequelae. In a Canadian study, 107 hospitalized children with post-vaccination thrombocytopenia were collected, a mean of 8.2 cases per year since 1996. The median age at presentation was 13 months (range 9 weeks–15.6 years). Seventy-seven cases followed administration of MMR vaccine; of these, 25 had received one or more additional vaccines as well. In two cases, a severe bleeding was observed, while the platelet count improved after treatment in 93 % of the pediatric patients within 3 months. Again, intravenous immunoglobulin ($N = 78$, 73 %) or corticosteroids ($N = 21$, 20 %) were the most used treatments [65].

Other vaccines

Mayboom et al. [58] also described five cases of hepatitis A virus (HAV) vaccine possibly linked with thrombocytopenia and purpura in three. Two cases were of a particular interest since in one patient, the reaction happened on two different occasions after HAV vaccination, and in the other patient, in which inactivated poliomyelitis vaccine and typhoid vaccine were administered simultaneously, arthralgia and influenza-like symptoms were also present.

Another case–control study explored the potential associations between adult ITP and various routinely administered vaccines. One hundred ninety-eight incident cases of ITP were compared with 878 age- and sex-matched controls. If, from one side, no evidence of an increase in ITP after vaccination in the previous 6 or 12 months was found, a higher risk for all vaccines was observed in the 2-month time window (OR 1.3). The vaccination against diphtheria–tetanus–pertussis–poliomyelitis was probably responsible for such increase (OR 1.5), although not statistically significant [66].

The first cases of ITP in humans after anti-rabies vaccine intramuscular injection have been described in two patients, a boy and a man of 12 and 53 years of age, respectively. They developed petechiae that, in the young boy, were associated with mild bleeding of the gums [67]. Interestingly, the association between such vaccine and thrombocytopenia in dogs is far more frequent since it represents up to 2–3 % of the cases. The reactivation of ITP was reported 2 weeks after a tick-borne encephalitis

vaccination in a previously treated 34-year-old woman who had achieved disease remission [68]. Vaccination against human papillomavirus virus (HPV) probably provoked the onset of prolonged menorrhagia and a low platelet count in a 16-year-old woman. Anti-platelet antibodies were found in this patient [69, 70].

A final observation may be derived from the data on a randomized, controlled trial to assess the immunogenicity and safety of a heptavalent combination vaccine including diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, Hib, and meningococcal serogroup C. Only one case of thrombocytopenia, considered severe by the investigator and with a potential causal relationship, was observed and resolved without sequelae. Nonetheless, reactogenicity and overall safety data were clinically acceptable in this trial [71].

Is it safe to vaccinate a patient with ITP?

The risk to develop ITP after vaccination opens an important question regarding the safety of vaccination in ITP patients. Limited and contrasting data are available in the literature. The great majority focused on the MMR vaccination, associated with the higher risk to develop ITP. The first published studies described the reactivation of ITP consequently to the immunization, regardless of the etiology. Accordingly, the authors suggested that MMR immunization should be contraindicated in subjects experiencing severe ITP after the first dose [72–75].

On the contrary, recent studies underlined the safety of vaccination in ITP subjects. The analysis conducted by Miller on 2001 showed clear evidence that children with ITP history prior to the first dose of MMR vaccine are not at an increased risk of an immunization-associated episode. Considering the 21 children with a first ITP episode prior to MMR immunization evaluated in the analysis, none of these children had a flare of the disease within 6 weeks of immunization. Only three children showed later a new ITP episode that was considered unrelated to the vaccination [76]. The results from the study conducted by Black on 2003 on data from the children registered in the UK General Practice Research Database showed a reactivation of the disease in three out of 52 ITP children and in all the cases were unrelated to MMR vaccination. Moreover, seven children with MMR-unrelated ITP were subsequently vaccinated without disease relapses [77].

More recently, Bibby et al. [78] in 2008 described three cases of children with chronic ITP, receiving immunization for MMR after the diagnosis of ITP. The authors concluded that MMR immunization is probably safe: No disease relapse was registered in the 6 weeks after immunization. Only a mild reduction in platelet count was noted, without symptoms development. These results were confirmed by the analysis of 92 ITP admissions in individuals who had received a second dose of MMR vaccine conducted by Stowe [79] in the same year. No evidences of an increased risk of ITP within 6 weeks of the second dose of MMR were identified.

According to the data reported in the literature, the recommendations published by the British Committee for Standards in Haematology [80] in 2003 underlined that the second dose of MMR vaccine in children developing ITP after the first dose is not contraindicated. However, the measure of the measles titers in children with chronic ITP before boosting with MMR is recommended, to decide whether a further dose is indicated. The risk/benefit *ratio* should be evaluated according with the incidence of infection in the specific community.

More recently, the Recommendations of the Advisory Committee on Immunization Practices (ACIP) first published on 1998 were revised. The committee agreed with the Hematology Task Force concerning the need to consider serological evidences of immunization, but suggesting also the re-immunization especially in seronegative children who are at risk to develop the infection [81].

Final remarks

Vaccines are one of the most striking discoveries in human history that changed dramatically life expectancy. Nonetheless, the occurrence of adverse events and autoimmune phenomena has been described following vaccination, and ITP may represent one of this. The occurrence of ITP after vaccination is, in most cases, a mild and treatment-responsive event. An important issue that must be underlined is that infections are much more likely to trigger ITP compared with their preventive vaccines. Nonetheless, vaccines are administered to larger populations of otherwise healthy subjects, and thus, the cumulative number of affected individuals may not be negligible. The recent description of a new syndrome, namely the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA), a new clinical entity entailing the association between a numbers of protean symptoms emerging after the exposure to adjuvants, put the physicians in challenges that the development of new immunization must face. Within ASIA syndrome, post-vaccination phenomena represent an important chapter. Thus, ITP onset after immunization may represent another additional autoimmune phenomenon of ASIA syndrome providing new data on the definition of pathogenic mechanisms.

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