

Infantile Bullous Pemphigoid Following Hepatitis B Vaccinations

Zafir Yaron¹, Zvulunov Alex² and Shoenfeld Yehoda^{1,3*}

¹The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Israel

²Medical School for International Health, Ben-Gurion University of the Negev, Beer-Sheva, Israel and Pediatric Dermatology Unit, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

³Sackler Faculty of Medicine, Incumbent of the Laura Schwarz-KipChair for Research of Autoimmune Diseases, Tel-Aviv University, Israel

Abstract

The development of infantile and childhood bullous pemphigoid following vaccination was already documented in several cases. This post-vaccination autoimmune phenomenon is part of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA).

A 4 months old female patient, presented with bullous skin rash, two months following her second inoculation with the hepatitis B vaccine (HBVv). In addition, during the appearance of the rash she received the second dose of hexavalent INFANRIX™-IPV/Hib vaccine (GSK), which was followed by irritability and fever. According to the clinical picture, biopsy result, direct immune fluorescent (DIF) and indirect immune fluorescent (IIF), a diagnosis of infantile bullous pemphigoid (BP) was determined. The patient was resistant to most conventional therapies.

We report a case of an infantile BP, which appeared following immunization with HBVv. This case depicts a temporal association between the appearance of autoimmune diseases and vaccines. The appearance of bullous dermatoses following vaccinations was reported in 14 case reports. The physicians should be aware of the option of such link and further inquiry is warranted.

Keywords: Vaccines; Bullous pemphigoid; Autoimmune/Inflammatory syndrome induced by adjuvants (ASIA); Autoantibodies; Autoimmunity

Introduction

Bullous Pemphigoid (BP) is an autoimmune blistering disease of the skin, which typically appears in the elderly with a peak incidence in the seventh decade [1]. The incidence of BP seems to be equal in both genders and no known ethnic or racial predilection was detected. Among adults the reported incidence of BP varies from 6.6 cases per million people per year in France and Germany to 43 cases per million people per year in the United Kingdom [2], among infants and children the incidence is much rarer [1-3].

BP is a chronic disease characterized by spontaneous exacerbations and remissions. Within 2.5 to 6.0 years about one-half of the treated patients are found in remission, nevertheless it might be fatal particularly when lesions are generalized [1,4-6].

The clinical manifestations of adult BP include tense blisters that following rupture leave shallow erosions. Oral cavity involvement is observed in 10 to 35% of the patients, mainly on the buccal mucosa. In infantile BP the blisters tend to occur more frequently on the palms, soles, face and rarely affect the genital area [4-6].

Histologically BP is characterized by a subepidermal blister with a predominant eosinophilic infiltrate [4-6].

The autoantibodies participating in BP typically react with two self-antigens the BP 230 (BP230 or BP antigen 1) a cytoplasmic protein and BP 180 (BP180 or BP antigen 2 or type XVII collagen) a transmembrane protein. Both antigens are part of the hemidesmosomes which belong to the dermo-epidermal adhesion complexes, promoting the adhesion in the epithelium (skin and mucous) [6,7].

The etiology of BP is poorly understood and it has been associated with an exposure to ultraviolet light, post radiation therapy, internal malignancies, other autoimmune diseases including rheumatoid arthritis, Hashimoto's thyroiditis, dermatomyositis, lupus erythematosus and autoimmune thrombocytopenia [5,8], in addition it has been associated with the exposure to systemic drugs such as furosemide, phenacetin, amoxicillin and ciprofloxacin [9].

In addition there are reports proposing the correlation of BP and vaccinations in adults [10-18] and young children (Table 1) [19-31]. The most common types of preceding vaccinations were influenza vaccines and the diphtheria tetanus pertussis but there are few reports on bullous pemphigoid following hepatitis B vaccination.

Herein, we describe a 4-month-old female child that following her second inoculation with hepatitis B vaccine (HBVv), developed bullous eruption compatible with BP which was refractory to most systemic therapies.

Case Presentation

A 4 month old female patient, presented with a new onset of bullous skin rash, which appeared two months following her second inoculation with HBVv. During the appearance of her rash she also received her second dose of hexavalent INFANRIX™-IPV/Hib vaccine (GSK) (directed against diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b) and developed irritability and fever.

The patient's medical history was unremarkable, the child was spontaneously delivered, on the 40th week of gestation, birth weight was 2900 gram. Parents originated from Yemen and Iran and her two elderly siblings were all healthy. No personal or familial history of autoimmune diseases.

On physical examination tense clear blisters and superficial

***Corresponding author:** Yehuda Shoenfeld, MD, FRCP, Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel, Tel: 972-3-5308070; Fax: 972-3-5352855; E-mail: shoenfel@post.tau.ac.il

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Fulfilled the criteria	ASIA	Time from vaccination to the appearance of symptoms	Vaccination	Age	Gender	Ref
1		unknown	DTP, Pollio	3 m	M	Oranje et al. [19]
1		5 h	DTP, Polio	4 m	M	Cambazard et al.[20]
1		1 d	DTP, Polio	3.5 m	M	Baykal et al. [23]
1		3 d	DTP, Polio, HBVv	3 m	F	Amos et al. [16]
1		2 w	DTP, Polio, HBVv	3 m	M	Xiao et al. [26]
1		4 w	DTP, Polio, HBVv	5 m	F	Khaled et al. [29]
1		1 w	DTP, Polio, HBVv, HiB	2 m	M	Merida et al. [25]
1		3 w	DTP, Polio, HBVv, HiB, MC, pneumococcus	2 m	F	Valdivielso-Ramos et al. [30]
1		8 d	DTP, Polio, HiB, pneumococcus	2 m	M	Hafiji et al. [28]
1		5 d	DTP, Polio, anti-influenza	2.5 m	M	Cunha et al. [21]
1		3 d	DTP	5 m	F	Toyama et al. [27]
1		9 d	BCG	5 m	F	Toyama et al. [27]
1		3 d	BCG	4 m	M	Hiroo et al. [22]
1		7 d	HBVv	12 y	M	Erbagci et al. [24]
1		14 d	DTP, pneumococcus	3 m	F	Barreau M et al. [31]

Table1: Infantile and childhood BP following vaccination.

erosions were observed on palms, soles, limbs, scalp, torso and genitalia (Figures 1-3) and the Nikolsky sign was absent. The rest of her physical examination was normal.

Histopathologic analysis from the edge of a blister demonstrated subepidermal bulla with mixed inflammatory infiltrates, including eosinophils (Figure 4). Direct immunofluorescence microscopy showed a linear deposition of IgG and C3 along the dermal-epidermal junction. An indirect immunofluorescence on the patient's serum, which was performed on monkey esophagus substrate revealed no IgA autoantibodies. Indirect immunofluorescence microscopy performed on 1 M sodium chloride-split human skin detected no circulating IgA antibodies. ELISA serologic findings detected antibodies for BP180 and BP230, with a very high reactivity against BP180. Complete blood cell count and routine chemical analysis demonstrated eosinophilia and increased IgE level up to 17,000 international units.

According to the clinical presentation, histopathological findings, DIF and IIF, a diagnosis of BP was determined.

The patient was initially treated with oral prednisone 2 mg/kg/day. Due to a limited effect - an adjuvant therapy with Intravenous immunoglobulin (IVIG) 2 gr/kg/day and diamino-diphenyl sulfone 4 mg/kg/day was administrated with a good response and temporary remission induction. During her follow-up multiple flares of the skin rash was observed. Therefore various immunosuppressive therapies were administrated, including pulsed methylprednisolone, methotrexate, mycophenolic acid, azathioprine and rituximab, however only partial remission could be achieved. At the age of 4 years a complete remission occurred while the patient was treated with oral methylprednisolone 2 mg/kg/day and methotrexate 0.75 mg/kg/week.

Initially her physical and mental developments were within normal range for age. However during the immunosuppressive treatment she suffered from severe failure to thrive, pathological fracture right femur, necrotizing enterocolitis, hypothyroidism and an event of sepsis which led to necrosis of her 3-5 right phalanges that had to be amputated.

Discussion

Childhood or infantile BP is rarely reported and the pathogenesis of this entity is still obscure. The disease usually begins within the first 6 months of life and this fact raised the possibility that the transfer of maternal IgG pemphigoid antibodies are the cause, however to date no antibodies have been detected in the serum of mothers [32]. In our present case a temporal association exists between the inoculation of the hexavalent vaccine and the development of the skin disease.

Vaccines are one of the most significant tools in today's preventive medicine. Thanks to vaccination programs that led to the eradication of various infectious diseases the mortality and morbidity of many children was reduced. HBVv was introduced at the early 80's, it is a recombinant vaccine that contains viral surface antigen emulsified within aluminum hydroxide serving as an adjuvant [33]. The INFANRIX™-IPV/Hib (GSK) vaccine was introduced in 2001, and is considered to be highly immunogenic and well tolerated [34]. It is an example of a combination vaccine that includes several antigens within one formulation that are effective in eliciting protection against various diseases [34]. The INFANRIX™-IPV/Hib (GSK) vaccine contains diphtheria toxoid, tetanus toxoid, three purified pertussis

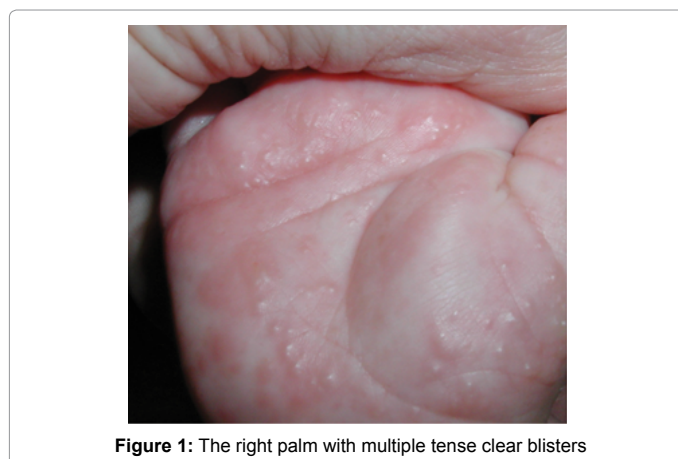


Figure 1: The right palm with multiple tense clear blisters



Figure 2: The left palm with multiple tense clear blisters and superficial erosions



Figure 3: The right sole with multiple tense clear blisters and superficial erosions

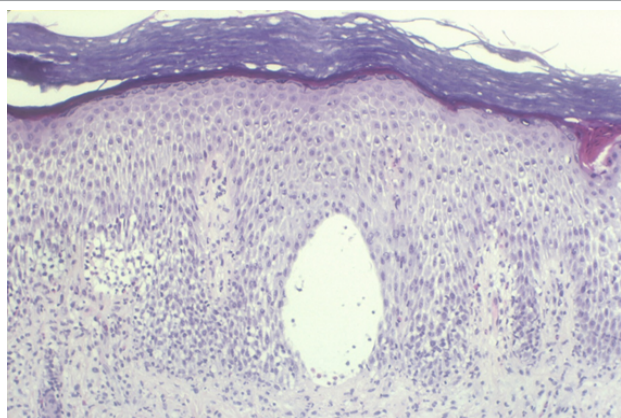


Figure 4: Histopathologic analysis from the edge of a blister demonstrated subepidermal bulla with mixed inflammatory infiltrates, including eosinophils

antigens adsorbed onto aluminum salts, inactivated poliovirus types 1, 2, and 3, and contains purified polyribosyl-ribitol-phosphate capsular polysaccharide of *Haemophilus influenzae* type b, covalently bound to tetanus toxoid [34].

Various human vaccines are incorporated with adjuvant such as aluminum. The role of adjuvants is poorly understood, however it is suggested to have a function in initiating inflammation response by the immune system [35]. In the past, immune adjuvant, were considered to be safe, however they were shown to induce immune mediated and autoimmune conditions [36-41].

The pathogenesis of autoimmune diseases is not well understood, however it is believed to be characterized by an interaction of many different factors. Those factors include genetic predisposition and the presence of an endogenous (immune system, hormonal milieu, etc.) and exogenous environmental factor, recently called “exposome”. The environmental factors include drugs, infectious agents, vaccines and adjuvants [42,43].

In the present case, a 4 month old healthy child developed a new onset of infantile BP two month following HBVv and in addition developed fever and irritability following her vaccination with INFANRIX™-IPV/Hib (GSK) vaccine, which was given during the appearance of her rash. The fact that an additional vaccine was given during the appearance of the rash itself might as well trigger the immune system and therefore causing the appearance of severe hard to treat disease.

The correlation between vaccination and autoimmune disease was previously suggested in diseases such as systemic sclerosis, chronic fatigue syndrome, fibromyalgia, transverse myelitis [33] systemic lupus erythematosus [44], anti-phospholipid syndrome, Guillain-Barré syndrome, Crohn’s disease, macrophagic myofasciitis, vasculitis, myelitis vaccinations and etc [45-51]. The same association was suggested for childhood and infantile BP [19-31].

In 2010 a syndrome termed “Autoimmune (Auto-inflammatory) Syndromes Induced by Adjuvants” (ASIA) was proposed as a term of defining autoimmune phenomena, which emerged following exposure to vaccine, silicone, tetramethylpentadecane, aluminum and other adjuvants [36]. This syndrome encompasses a wide variety of adjuvant induced conditions from vague non-specific manifestations to well defined autoimmune diseases. The criteria include four major criteria exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations, the appearance of ‘typical’ clinical manifestations removal of inciting agent induces improvement and typical biopsy of involved organs and four minor criteria the appearance of autoantibodies or antibodies directed at the suspected adjuvant, other clinical manifestations, specific HLA and involvement to autoimmune disease [36]. The present case fulfilled the ASIA criteria as she was exposed to vaccination, had a typical skin biopsy and developed an autoimmune disease.

Considering the characteristic features of infantile BP following vaccination, (Table 1) described in the literature, most cases at the time of diagnosis were of few month ranging from 2.5 to 5 months, however one patient was 12 years old. Time from vaccination to the appearance of symptoms ranged from hours and up to a month. The most common reported vaccine to be associated with infantile BP was the hexavalent followed by HBV vaccine and BCG when applying the ASIA criteria to those patients all fulfilled the ASIA criteria, and therefore were diagnosed with ASIA syndrome.

The clinical presentation of the present case was similar to what is reported in infantile BP [52] as the tense clear blisters and superficial erosions were distributed mainly on her palms and soles.

Infantile BP generally responds to corticosteroid, diamino-diphenyl sulfone or sulfapyridine. However patients that are nonresponsive to those conventional treatments are administered with alternative treatments such as IVIG [1,26,52-54], mycophenolate mofetil or Rituximab [1]. Our case was resistant to a variety of combination immunosuppressive therapies till the age of 4 years when remission occurred while the child was treated with methylprednisolone and

methotrexate.

Conclusion

Infantile BP is a rare entity, and its management is often problematic. The plausible role of exogenous factors, such as vaccinations, should be further investigated.

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