

# Henoch-Schönlein Purpura Post-Influenza Vaccination in a Pediatric Patient: A Rare but Possible Adverse Reaction to Vaccine

Rachael Kantor MD<sup>1\*</sup>, Alex Galel MD<sup>1\*</sup>, and Shraga Aviner MD<sup>1,2</sup>

<sup>1</sup>Medical School for International Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

<sup>2</sup>Department of Pediatrics, Barzilai University Medical Center, Ashkelon, Israel

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Influenza vaccinations have been accused of being a cause or trigger for several diseases and other medical phenomena, although a causative relationship has not been clearly established in most cases. The etiology of Henoch-Schönlein Purpura (HSP), a small-vessel systemic vasculitis in children, remains elusive; its pathogenesis is listed as an immune-mediated vasculitis, associated with IgA deposition. Seventeen cases of HSP post-vaccination with the influenza vaccine have been reported in a literature review in 2016 [1] as well as two single cases reported after. These reports, however, describe severe forms of the disease, while our patient had a milder, more benign presentation of vasculitic disease, post-influenza vaccination.

## PATIENT DESCRIPTION

A healthy 4-year-old girl, with a history of seasonal urticaria, reported to the emergency department (ED) 4 days after the appearance of rash and bruising. The rash broke out initially on her back and was present on the chest, arms, and

cheeks for 2 days before concentrating in the lower extremities. She did not respond to antihistamine administration, and as the rash persisted, the child was referred to the ED.

The parents reported that she had had no recent illness or symptoms, such as episodes of fever, joint pain, cough, runny nose, diarrhea, or changes in urine output. The young patient had not come in contact with infectious diseases, changes in diet, recent travel, or alterations in her normal routine, and had never experienced a rash of this kind before. However, she had received her first-ever seasonal flu vaccine 8 days prior to the appearance of the rash. On physical examination, the eruption looked like a mixture of hives and bruises [Figure 1].

The rash was not pruritic or raised and it blanched in response to pressure. The rest of the physical examination was unremarkable. Urinalysis was positive for microhematuria (RBC + 1). This symptom, in combination with her purpuric lesions and age, established a clinical diagnosis of HSP [2]. The sequelae of HSP was explained to the patient's mother, who was instructed to bring her daughter back to the ED if she noticed symptoms of abdominal pain, arthralgias, change in emotional state, or gross hematuria. A follow-up appointment was scheduled one week later at the pediatric day care center.

On follow up, the patient was active and cooperative, with no fever. Complete

resolution of the rash was noted 3 days prior to the visit, with no residual signs or hematomas present. Arthralgias, abdominal pain, and gross hematuria were negated, and, according to the mother, the 4-year-old had exhibited no behavioral changes since initial presentation. No abnormalities were revealed on physical exam. Complete blood count with differential count, creatinine, blood urea nitrogen, complement panel (C3, C4), rheumatic panel, immunoglobulins, coagulation studies and urinalysis were normal. The patient's mother was advised that her daughter should have a weekly urinalysis for the next 6 weeks and was instructed to return to the ED if new symptoms developed.

## COMMENT

Our patient presented with an isolated mild form of HSP 8 days after receiving her first dose of ordinary seasonal flu vaccination. The diagnosis of HSP was clinical. Nelson's Textbook of Pediatrics defines HSP by the presence of two or more of the following criteria: palpable purpura in the absence of thrombocytopenia, bowel angina, diagnostic biopsy showing IgA deposits in the vessel walls, or inclusion within the pediatric age group [2]. Our patient met the criteria for palpable purpura in the absence of thrombocytopenia (PLT 369 K/ $\mu$ l) and, at 4 years old, she was within the pediatric age group. Although other sources

\*The first two authors contributed equally to this manuscript

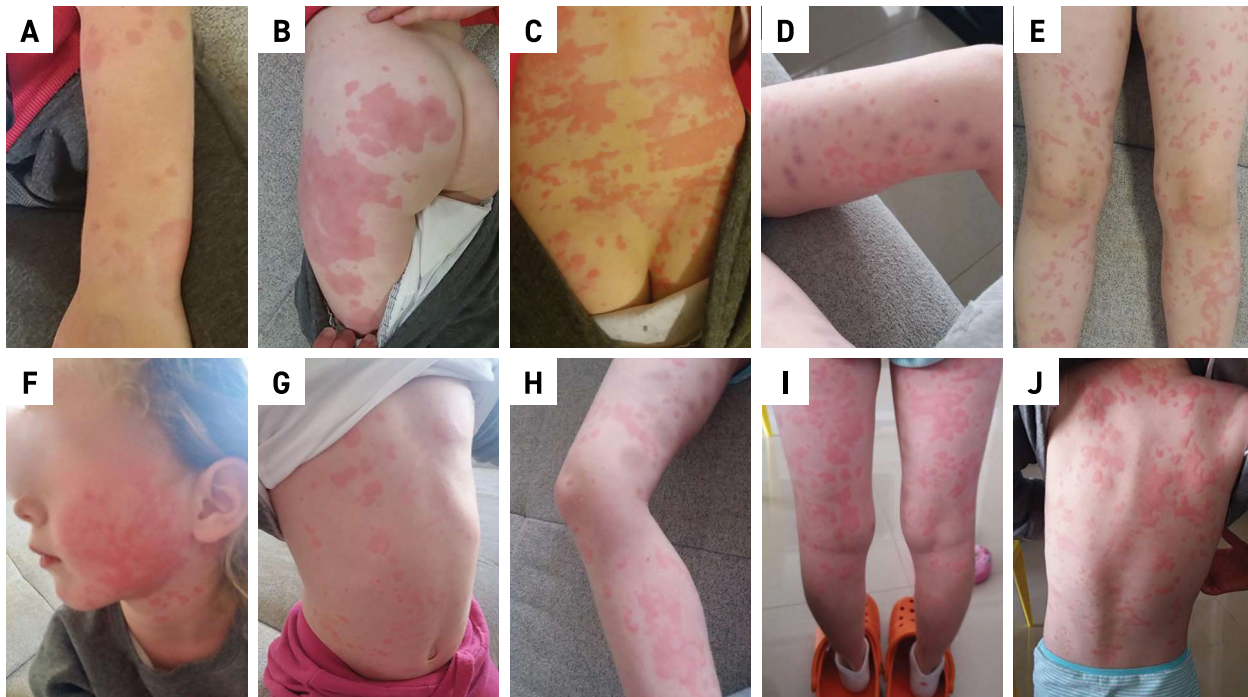
**Figure 1.** Photo timeline of rash progression prior to emergency department presentation (day of disease)

Day 1: left arm [A] and buttocks and left thigh [B]

Day 2: back [C] and left leg [D]

Day 3: legs (front) [E], Left cheek and neck [F], abdomen [G], right leg [H], legs (back) [I]

Day 4: Back [J]



(the EULAR/PRINTO/PRES criteria for HSP [1]) use more stringent criteria for diagnosis, the American College of Rheumatology upholds the same classification criteria as Nelson's, noting that while these criteria were developed for use in research, they are not valid for clinical diagnosis [3].

Although our patient's rash was initially considered to be seasonal urticaria, its duration and distribution pattern, paired with its evolution of a purpuric nature and microhematuria, ruled this out as a possible etiology of disease. The clinical picture of purpura, normal platelet count, and normal coagulation test results were positive criteria for vasculitic disease. Urticarial vasculitis and other leukocytoclastic vasculitides were, therefore, considered in our differential diagnosis. These diseases typically present in older age groups with pruritus or pain [2], which were not seen in this patient. This information further

supports the diagnosis of HSP over other vasculitic diseases.

Initial laboratory workup for confirmation in this case was limited. The connection between the influenza vaccine and the HSP reaction was only considered after the patient had been discharged from the ED. Had complementary tests been performed, such as erythrocyte sedimentation rate, C-reactive protein, and anti-neutrophilic cytoplasmic antibodies (ANCA) on presentation, further supporting evidence for HSP might have been available. It is likely that the patient would have presented with lowered C3 and/or C4, elevated inflammatory markers and possible positive ANCA [2], although it is important to stress that none of these results are essential for diagnosis. Due to our patient's age and the benign nature of the findings, we deemed it prudent to avoid invasive procedures; therefore, a tissue biopsy for histopathology was not considered.

It has been suggested that immune mediated responses to influenza antigens or other materials in the vaccine such as gelatin, ovalbumin, or phosphate buffers might play a role in the vasculitic response [3]. It has also been suggested that the structural similarity of the influenza antigens and the vaccine proteins may activate the same autoimmune reaction [4]. Hence, it is possible that vasculitis occurs in the form of complex immune mediated vessel wall damage, autoimmune activation of B and T cells by molecular mimicry and superantigens, or perhaps by a direct invasion of the virus into endothelial cells [4]. Scrutiny of the Ministry of Health registries in Israel revealed no similar reports related to the same batch of vaccine or any other batches, since the advisory committee's recommendation for universal influenza vaccination in Israel in March 2011. In Israel, approximately 1.7 million people receive the vaccine every year, 21% of

whom are aged 6–59 months. Being the first reported HSP post-flu vaccination case might be the result of under-reporting. However, one could speculate that such a low rate implies that this side effect may be a result of some immune predisposition of the host to a reaction triggered by any of the vaccine components rather than a toxic general effect of the vaccine components.

Influenza vaccines are reformulated and administered on a yearly basis. There are opposing theories on how this affects recurrence of reaction. Zafrir and authors [4] hypothesized that the risk for recurrent reactions increases as the antigens within the vaccine are altered to meet changing environmental requirements. In contrast, Ledford and colleagues [5] suggest that yearly modification of antigens could actually lower the risk of a recurring reaction since the reaction may be antigen specific. Although immunologic reactions may become more severe with re-administration of a vaccine, there is no definitive conclusion regarding contraindication to vaccine re-administration.

A dearth of reports of repeated HSP post-flu vaccination could be the result of:

- Reluctance on the part of parents and/or medical staff to revaccinate in the

event of indecisive recommendations

- Repeated HSP post-flu vaccination is very rare or does not exist due to changes in vaccine antigenicity each year
- The first dose of the vaccine generated a tolerance to the vaccine antigens so as to cause no adverse immunologic reactions

Our young patient made a complete recovery and to date enjoys normal renal function. In this case, the risk of contracting influenza is higher than the likelihood of the occurrence of HSP; however, reactions vary, as shown in published cases [1]. Of the previously reported cases of HSP following influenza vaccination, only two reported chronic renal complications [1]. We recommend caution when administering future influenza vaccines to those who have had HSP post-influenza vaccination, and patients should be informed that they may experience similar adverse reactions upon re-administration of the vaccine. We recommend that those with previous reactions use vaccines formulated by a different manufacturer [5].

#### CONCLUSIONS

As widespread compliance with influenza vaccination increases among the juvenile population, it is important to gain

further insight into post-immunization vasculitic reactions. Current understanding of the association, if it is a real one, is limited by insufficient research to date. It is therefore important that in the future similar cases be identified and reported to broaden the available information.

#### Correspondence

Dr. S. Aviner

Dept. of Pediatrics

Barzilai University Medical Center, Ashkelon 7830604,

Israel

Fax: (972-8) 674-5648

email: aviners@bmc.gov.il; aviners@gmail.com

#### References

1. Liu JY, Wu QS, Liu M, Wang L, Gao YH, Li SS. Henoch-Schönlein purpura nephritis following influenza vaccination: a case report and review of the literature. *Southeast Asian J Trop Med Public Health* 2016; 47 (5): 945-50.
2. Ardoin SP, Fefs E. Henoch-Schönlein purpura. Nelson Textbook of Pediatrics, vol. XVI. 20th ed., Philadelphia, PA: Elsevier; 2016, p. 1216-7.
3. Watanabe T. Henoch-Schönlein purpura following influenza vaccinations during the pandemic of influenza A (H1N1). *Pediatr Nephrol* 2010; 26: 795-8.
4. Zafrir Y, Agmon-Levin N, Shoenfeld Y. Post-influenza vaccination vasculitides: a possible new entity. *J Clin Rheumatol* 2009; 15 (6): 269-70.
5. Ledford DK. Henoch-Schönlein Purpura and Influenza Vaccine. *J Allergy Clin Immunol Pract* 2017; 5: 210.

#### Nothing happens unless first a dream.

Carl Sandburg (1878–1967), American writer and poet, winner of three Pulitzer Prizes: two for his poetry and one for his biography of Abraham Lincoln

#### Capsule

### The second way to anticommensal IgA

Mammals rely on secretory immunoglobulin A (SIgA) at the intestinal surface to maintain a homeostatic relationship with the commensal gut microbiota. B lymphocytes differentiate into IgA-producing plasma cells through a thymus-dependent pathway that depends on the B cell protein CD40 transducing a signal from CD40 ligand on T cells. **Grasset** and colleagues investigated the contribution of a receptor called TACI found predominantly

on B cells to an alternative, thymus-independent pathway of plasma cell differentiation. The mucosal immune system was found to use parallel pathways dependent on either CD40 or TACI to provide B cells the help needed to generate SIgA capable of binding commensal bacteria.

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Eitan Israeli