

CASE REPORT

Erythema Multiforme Following Hepatitis A and Pneumococcal Vaccinations

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Erythema multiforme (EM) is a rare cell-mediated immune response characterized by target or iris patches or plaques that present symmetrically on the extremities. This condition may be associated with pruritus but is usually self-limited and spontaneously resolves within 5 weeks of onset; prodromal symptoms are rare. Several known cases have been linked to vaccination, but many vaccines used in pediatric care have been reported as causative agents of EM. This case study offers an association of EM following administration of the hepatitis A and pneumococcal vaccines.

INTRODUCTION

Erythema multiforme (EM) is a condition characterized by targetoid plaques that manifest on the skin and can involve mucosal membranes. If one or no mucosal membranes are involved, the case is classified as EM minor. Those involving two or more are labeled as EM major [1]. EM begins as red or pink macules that develop papules that can enlarge into plaques. These plaques typically have a round shape with a central region that becomes darker red or dusky brown several days later [2]. Patients may have multiple papules and plaques at different morphological stages, some with central vesicle ulceration. EM is named for its various morphologies that arise during its course. Lesions appear symmetrically distributed, primarily on the extremities and can manifest on the palms of the hands and soles of the feet [2-5]. EM usually resolves spontaneously within several weeks [2,5].

EM is caused by a cell-mediated immune response triggered by certain infections, drugs, and conditions. It is considered acute and self-limiting [2], and rarely has prodromal symptoms [2,6]. EM was once thought to be on the same pathologic spectrum as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. However, EM is currently considered a separate entity with a distinct etiology, pathophysiology, and clinical course [4]. EM can be distinguished from urticaria multiforme given its clinical history. A single EM lesion typically resolves within several days, while urticaria multiforme plaques resolve within 24 hours [5]. Urticaria multiforme does not involve the mucosal or acral regions [4,7-9]. Unlike EM, urticaria multiforme commonly results in facial or acral edema and dermographism [4]. Other conditions for the clinicians to distinguish from EM include Serum-Sickness-Like-Reaction (SSLR), Urticarial Vasculitis, and Acute Hemorrhagic Edema of Infancy (AHEI). SSLR can

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Abbreviations: EM, Erythema Multiforme; SSLR, Serum-Sickness-Like-Reaction; AHEI, Acute Hemorrhagic Edema of Infancy.

Keywords: Erythema Multiforme, Hepatitis A Vaccine, Pneumococcal Vaccine, Pediatric, Cutaneous Reaction to Vaccine, Vaccine Reactions

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Figure 1. Targetoid plaques on a 15-month-old, 12 days after vaccination. A. Targetoid plaques on left upper extremity. **B.** Targetoid plaques, excoriated and crusted, on left lower extremity.

commonly occur with high fever, arthralgias, myalgias, and lymphadenopathy [4]. These systemic symptoms are generally absent in EM. Urticarial vasculitis can present as hives that manifest concomitantly with symptoms such as facial or acral edema, arthralgias, and primarily affects adults [4]. AHEI primarily affects pediatric patients under the age of 2 and has been reported to occur after vaccinations with similar presentation as EM. Unlike EM, 50% of AHEI cases have been reported with fever, and commonly with nonpitting edema mainly on the face and ears [10].

Most EM cases are associated with infections (90%) [1,11,12], especially with herpes simplex virus (50-80% of cases) [2,6,11]. Various drugs and vaccines have also been reported as causative agents [1,2,6]. EM is rare and has an annual incidence of less than 1% [6], and an even lower incidence of vaccine-induced EM exists. We report a case of a 15-month-old toddler who developed EM following administration of the first dose of the hepatitis A vaccine and the fourth dose of the pneumococcal vaccine.

CASE STUDY

An otherwise healthy 15-month-old boy presents to dermatology with a 12-day history of a generalized eruption consisting of raised pruritic plaques (Figure 1). Several plaques had central and linear erosions. The patient had no other symptoms and was afebrile. The parents of the patient report no relevant changes in diet, linen, or environment, and no drugs had been administered prior

to the outbreak, but the patient had recently received an initial dose of hepatitis A vaccine and the 4th dose of pneumococcal vaccine.

The rash was localized to lower extremities and temples 5 days post-vaccination, with an onset 3 days post-vaccination. Pediatricians advised applying hydrocortisone 1% cream to the plaques and giving colloidal oatmeal baths.

Eight days post-vaccination new lesions formed. An oral H1 histamine antagonist, triamcinolone 0.1%, and mupirocin 2% ointments were added to the patient's treatment.

Eleven days post-vaccination, new lesions continued to arise. The child was prescribed prednisone (15mg/5mL solution, 1mg/kg/dose, BID PO for 5 days) and referred to dermatology.

During the physical examination, the patient was alert, afebrile, and appeared to be a healthy growing toddler. Physical examination revealed multiple well-defined, circular, erythematous plaques with a darker central vesicle on the extremities. Trunk, mucosal surfaces, and the palmoplantar regions were spared. Due to the history, physical findings, and the correlation of the eruption following vaccination, the patient was diagnosed with EM. A skin biopsy was not performed due to the patient's age and pathognomonic clinical findings. Sixteen days post-vaccination, following a 10-day course of oral prednisone, most of the lesions had resolved with no new outbreaks.

DISCUSSION

Vaccine-induced EM is rare, accounting for a small sample of all EM cases, yet in a study conducted by Zoghaib et al., vaccines account for a much higher rate of EM cases in pediatric patients (3.9%) and infants (47.3%) [1]. The trend in this demographic could be partly attributed to higher vaccination rates in pediatric patients and fewer exposures to other causative agents such as drugs and pathogens when compared to older patients. Diagnosis is usually based upon clinical findings. Histopathologic examination of a skin biopsy, when obtained, shows a lymphocytic infiltrate at the dermal-epidermal junction associated with basal vacuolization and dyskeratotic or apoptotic keratinocytes. A subepidermal bulla may form.

Despite a low incidence of vaccine-induced EM, most vaccines used in pediatric care have been reported to cause EM [1], frequently including the following: Diphtheria-tetanus-pertussis [1,2,12-14], hepatitis B [1,2,5,12-14], HPV [1,12,13], measles-mumps-rubella [1,5,12,13], meningitis [2,5,13,14], and smallpox [1,2,5,12-14]. While EM could have been induced idiosyncratically in the case presented, the onset of the symptoms and the duration of the condition are consistent with other case reports, especially for vaccine-induced EM and pediatric EM. Although it would be difficult to determine whether the combination of the two vaccines or one alone caused the eruption, adverse effects following immunizations tend to decrease with subsequent booster doses [14], which could suggest the pneumococcal vaccine may be uninvolved. However, it should be noted that the pneumococcal vaccine has been reported as a causative agent [1,5,12,13]. Clinicians should be aware of the condition as it occurs in children in the setting of increasing numbers of mandatory and recommended vaccines. EM has been reported in adults vaccinated with mRNA BNT162b2 [3,15], mRNA-1273 SARS-CoV-2 [16], and CoronaVac [17]. A similar pattern is therefore expected in young children and infants as they become eligible for COVID-19 vaccines. Based on the evidence that EM is a rare and self-limited condition and what is known about adverse effects following vaccination, we believe the benefits of vaccination far outweigh the risks.

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