BRIEF COMMUNICATION

Case Series of Three Infants with Erythema Multiforme Following Hepatitis B Vaccination

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1. Introduction

Erythema multiforme (EM) is an acute, self-limited, sometimes recurring mucocutaneous condition characterized by distinctive target lesions, and it has been associated with infections, accounting for up to 90% of cases, as well as with drugs, and other triggers. Most cases of EM occur in children, adolescents, and young adults, but rarely occur in neonates and infants. Here, we report three infants in whom EM developed following hepatitis B vaccination.

2. Case series

Three male infants were admitted over the past 2 years with EM following hepatitis B vaccination. They were born at full-term gestation and had a mean age of 37 days at presentation. All had the main complaints of rash with preceding hepatitis B vaccination administered 1–5 days earlier, and fever beginning on the day of presentation, with no localizing symptoms or risk factors for infection. On examination, they had raised targetoid lesions over the face, chest, abdomen, and limbs. Figures S1 and S2 depict the targetoid rash in the first two infants.

A full sepsis work-up was performed in each infant. The fever settled within 1 day of admission in all of the infants, and was attributed to postvaccination fever, with negative microbiological investigations. The skin rash was clinically diagnosed by the dermatologist as EM secondary to hepatitis B vaccination, in view of the temporal relationship between the development of EM and the vaccination, and in the absence of other known causes of EM. No skin biopsies were performed. The rash lasted for a mean duration of 2 weeks. There were no recurrences of EM in two of the infants, with a follow-up appointment being scheduled for the third infant. Table 1 summarizes the patient characteristics and investigation results of the three infants.

3. Discussion

Although the pathophysiology of EM is still not completely understood, it is in part due to a type IV hypersensitivity reaction that can be triggered by numerous factors, including infections (for which the most common organisms are herpes simplex virus types 1 and 2 and mycoplasma pneumoniae), as well as drugs such as nonsteroidal anti-inflammatory drugs, antiepileptics, and antibiotics. Vaccinations have also been implicated in EM. In particular, there have been several adult cases of EM following hepatitis B vaccination, as well as a similar case in a 1-month-old infant. It is speculated that the hepatitis B surface antigen (HBsAg) may be responsible for the reaction, where specific immune stimulation postvaccination can induce the formation of immune complexes as well as stimulation of T cells.

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<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (d)</th>
<th>Gender</th>
<th>Rash Characteristics</th>
<th>Other presenting symptom(s) on admission</th>
<th>Interval between hepatitis B vaccination &amp; onset of rash (d)</th>
<th>Reactions to previous vaccinations</th>
<th>Investigation results</th>
<th>Clinical diagnosis of erythema multiforme (EM)</th>
<th>Treatment</th>
<th>Duration of hospitalization (d)</th>
<th>Duration of rash before complete resolution (wk)</th>
<th>Recurrence of EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Male</td>
<td>Rash for 3 d</td>
<td>Nil Bacillus Calmette-Guerin &amp; 1st dose of hepatitis B vaccinations were given at birth with no issues</td>
<td>Fever of up to 38.3°C for 1 d</td>
<td>Lesions remained fixed over 24 hours</td>
<td>No blistering or necrosis</td>
<td>No mucosal involvement, angioedema, or dermatographism</td>
<td>Clinical diagnosis of EM made by dermatologist</td>
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<tr>
<td>2</td>
<td>2</td>
<td>No recurrence of EM, even with his 3rd dose of hepatitis B vaccination at 6 mo of age &amp; other vaccinations (rotavirus, pneumococcal, &amp; combined diphtheria, tetanus, polio, pertussis &amp; haemophilus influenzae type b [DTaP/IPV/Hib])</td>
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**Blood investigations**

1. Haemoglobin (Hb) 12.7 g/DL (normal range 9–14 g/DL), white blood cell count (WBC) 8.43 x 10^9/L (normal range 5–15 x 10^9/L), platelet count 414 x 10^9/L (normal range 150–450 x 10^9 L)
2. C-reactive protein (CRP) 20.5 mg/L (normal range 0–5 mg/L)
3. Liver function test normal

**Microbiological investigations**

1. Blood, urine & cerebrospinal (CSF) bacterial cultures negative
2. Throat swab & CSF for enterovirus (EV) PCR negative
3. CSF for herpes simplex virus (HSV) PCR negative
4. Throat swab for mycoplasma pneumoniae PCR negative
5. Nasopharyngeal aspirate for respiratory viruses antigen negative

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</thead>
<tbody>
<tr>
<td>2</td>
<td>37</td>
<td>Male</td>
<td>Rash for 1 d</td>
<td>Nil Bacillus Calmette-Guerin &amp; 1st dose of hepatitis B vaccinations were given at birth with no issues</td>
<td>Clinical diagnosis of EM made by dermatologist</td>
<td>Full sepsis work-up performed &amp; empirical Ampicillin &amp; Gentamicin started</td>
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<td></td>
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<td></td>
<td>Raised targetoid lesions over face, chest, abdomen &amp; limbs</td>
<td>Fever of up to 38°C C for 1 d</td>
<td>Blood investigations (1) Hb 10.7 g/DL, WBC 12.59 x 10^9/L, platelet count 508 x 10^9/L (neutrophils 39%, lymphocytes 55%, monocytes 5%), CRP 9.7 mg/L (2)</td>
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<td>Lesions remained fixed over 24 hours</td>
<td>No blistering or necrosis No mucosal involvement, angioedema, or dermatographism</td>
<td>Microbiological investigations (1) Blood, urine &amp; CSF bacterial cultures negative (2) Throat swab &amp; CSF for EV &amp; HSV PCR negative (3) Urine &amp; CSF for cytomegalovirus PCR negative</td>
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<td>3</td>
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<td>Male</td>
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<td>Raised targetoid lesions over face, chest, abdomen &amp; limbs</td>
<td>Fever of up to 38.5°C C for 1 d</td>
<td>Blood investigations (1) Hb 10.3g/DL, WBC 17.58 x 10^9/L (neutrophils 39%, lymphocytes 55%, monocytes 5%), platelet count 667 x 10^9/L (2) CRP 9.2 mg/L (3) Liver function test normal</td>
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lymphocytes, which can then react with peptides shared by HBsAg and keratinocytes. The lack of reaction with the subsequent vaccination dose could be attributed to immune maturation.

Other possible differentials include urticaria multiforme, where annular wheals with an ecchymotic center may be present, but these lesions typically last for <24 hours, are pruritic, and are associated with dermatographism and facial or acral edema. Acute hemorrhagic edema of infancy is a distinctive leukocytoclastic vasculitis affecting infants younger than 6 months, often following a viral infection and presentation is often dramatic, with large targetoid purpuric lesions localized to the cheeks, ears, and acral regions, and facial and limb edema is often present.

Diagnosis of erythema multiforme is usually clinical, but skin biopsy can help confirm the diagnosis. Histology typically shows a lymphohistiocytic infiltrate along the dermoepidermal junction and surrounding blood vessels, basal epidermal cell vacuolar degeneration, scattered necrotic keratinocytes, and lymphocyte exocytosis. Subepidermal clefting and vesiculation may occur due to extensive basal cell vacuolar degeneration.

Management of EM is largely symptomatic, and topical low potency corticosteroids may be helpful. Parents should be reassured that EM following immunization is not a contraindication for subsequent doses of the same vaccine. Although active monitoring during the subsequent doses may be considered, no specific measures may be needed, given that no recurrence occurred in two of our cases. In an Australian study of 421 children with a history of an adverse event following immunization (AEFI), 33 children had a skin rash following immunization, and none had a recurrence following re-immunization.

4. Conclusion

These three cases highlight a possible temporal association between EM and hepatitis B vaccination, although there was no evidence of causation. Clinicians who vaccinate children on a regular basis should be aware of this potentially rare AEFI, as this may help avoid unnecessary investigations in evaluating the etiology of EM. Parents should be reassured that EM following immunization is not a contraindication for continuing the vaccination course, and that the benefits of vaccination outweigh its risks.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References


Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pedneo.2015.03.012.