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CASE REPORT

Neonatal erythema multiforme associated with a rotavirus infection: A case report

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Abstract

BACKGROUND

Erythema multiforme (EM) is an extremely rare condition in neonates, and studies suggest its association with certain infections and neonatal vaccinations; however, few specific etiological agents have been identified. Rotavirus, a common pathogenic gastrointestinal virus in the neonatal period that is preventable *via* vaccination, has not been identified as a possible etiology. We report the case of a neonate who was referred for skin lesions presenting as EM, where a meticulous workup identified rotavirus as the sole causative agent.

CASE SUMMARY

A 14-day-old male infant was admitted to our hospital with a 1-day history of skin lesions. No medical history or medication intake was recorded. Except for the complaint of skin lesions, the caregivers denied any abnormal symptoms. Multiple tests, including routine laboratory evaluations, were performed to identify the cause of skin lesions. Serological tests for Immunoglobulin M for Toxoplasma, Rubella, Cytomegalovirus, Herpes Simplex Virus, and Epstein-Barr virus viral-capsid antigen were all negative. Multiple polymerase chain reaction (PCR) tests for respiratory viruses and bacterial pathogens were negative (including the severe acute respiratory syndrome coronavirus 2). Multiple PCR tests for gastrointestinal viruses and bacterial pathogens demonstrated evidence of rotavirus infection. No growth was reported in the blood and urine cultures. The patient received intravenous fluids for hydration; meanwhile, no other medications were prescribed. The lesions improved rapidly without specific treatment, and full recovery was achieved within a week.

CONCLUSION

The possibility of rotavirus, a major cause of pediatric gastrointestinal infections, being a trigger for neonatal EM should be considered.

Key Words: Erythema multiforme; Gastrointestinal diseases; Neonate; Rotavirus; Skin abnormalities; Case report

Core Tip: Various etiologies, including infections, medications, malignancy, and immunization, are responsible for erythema multiforme (EM). EM is extremely rare in the neonatal period. Some potential causes have been reported in the literature, including hepatitis B vaccination and certain infections. As demonstrated in the current case, rotavirus, which is a common pathogenic gastrointestinal virus in the neonatal period that is preventable *via* vaccination, could be a cause of EM. Physicians should make their best effort in scrutinizing the etiology of the illness.

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INTRODUCTION

Erythema multiforme (EM) is extremely rare in the neonatal period[1,2]. Although the neonatal period may be a challenging time for newborns, medications are rarely used in healthy babies. Therefore, the etiology of neonatal EM is not easy to identify. Whilst attending physicians may not recognize the cause of the disease, some potential causes have been reported in the literature: Vaccination against hepatitis B, tuberculosis [Bacille Calmette-Guérin (BCG)] and certain infections[3-7].

Rotavirus is a common pathogenic gastrointestinal virus in the neonatal period that is preventable *via* vaccination. Two live, attenuated oral rotavirus vaccines are licensed for use and implemented globally, contributing to the overall decrease of the disease burden, despite several concerns about adverse events and safety[8]. Despite the fact that diarrhea, vomiting, and fever are known to be the main symptoms of rotavirus infection, there have been reports of uncommon cutaneous manifestations[9], which include, but are not limited to, (maculopapular) exanthema, Gianotti-Crosti syndrome, and acute infantile hemorrhagic edema[10,11]. To the best of our knowledge, rotavirus nor vaccination against rotavirus has been identified as a cause of EM. Here, we present a case of neonatal EM associated with rotavirus infection.

CASE PRESENTATION

Chief complaints

A 14-day-old male infant was admitted to our hospital with a 1-day history of skin lesions.

History of present illness

The infant was born at a gestational age of 38 wk and one day, with a birth weight of 2890 g. The mode of birth was cesarean section due to prior cesarean delivery, with no problematic events during the pregnancy, according to the mother. The baby was fed formula milk without attempting breastfeeding, at the mother's discretion. The first dose of the hepatitis B vaccine, a routine global procedure, was administered on the day of birth.

History of past illness

No medical history or medication intake was recorded. Except for the complaint of skin lesions, the caregivers denied any abnormal symptoms.

Personal and family history

No pertinent personal or family history was noted. Paternal and maternal history of human papillomavirus and/or hepatitis-related infections was denied.

Physical examination

On examination, the baby appeared well and active. Initial vital signs were as follows: Heart rate: 146 beats/min; respiration rate: 46 breaths/min; body temperature: 37.3 °C; and pulse oximetry saturation: 98%. His entire body was covered with erythematous papules (Figure 1A), with annular or target-like lesions observed mainly on the lower extremities (Figure 1B). The oral and anal mucosal membranes were intact. No other abnormalities were observed.

Laboratory examinations

Multiple tests, including routine laboratory evaluations, were performed to identify the cause of skin lesions (Table 1).

Table 1 Laboratory findings from a neonate with erythematous multiforme associated with rotavirus infection

Test	Results (normal range)
Complete blood cell count	
White blood cell (/μL)	7450 (9100-34000)
Neutrophil (%)	32.7 (54.0-62.0)
Lymphocyte (%)	56.5 (25.0-33.0)
Eosinophil (%)	1.6 (1.0-3.0)
Hemoglobin (g/dL)	12.0 (15.0-24.0)
Platelet (/μL)	649000 (150000-400000)
Chemical	
Aspartate aminotransferase (IU/L)	32 (22-71)
Alanine aminotransferase (IU/L)	28 (10-40)
BUN (mg/dL)	8.7 (3.0-12.0)
Creatinine (mg/dL)	0.30 (0.03-0.50)
Albumin (g/dL)	3.8 (1.9-4.9)
hs-CRP (mg/dL)	0.06 (0.08-1.58)
Total bilirubin (mg/dL)	2.86 (< 22.0[1])
Urinalysis	
Protein	Negative
White blood cell (/HPF)	0-1
Red blood cell (/HPF)	0-1
Coagulation	
Prothrombin time (international normalized ratio)	0.85 (< 1.2)
Activated partial thromboplastin time (s)	27.1 (25.6-33.4)
Antibodies	
Toxoplasma IgG/IgM	Negative/Negative
Rubella IgG/IgM	Equivocal/Negative
Herpes Simplex Virus IgG/IgM	Positive/Negative
Cytomegalovirus IgG/M Ab	Positive/Negative
Epstein-Barr virus viral-capsid antigen IgM Ab	Positive/Negative
PCR	
Respiratory panel (virus[2]/bacteria[3]) (nasopharyngeal swab)	Negative/Negative
Acute diarrhea panel (virus[4]/bacteria[5]) (stool)	Rotavirus/Negative
Severe acute respiratory syndrome coronavirus 2 (nasopharyngeal swab)	Negative

[1]Hour-specific thresholds for phototherapy in newborns 38 wk gestation with unconjugated hyperbilirubinemia in the absence of neurotoxicity risk factors.
[2]Adenovirus, Influenza A/B virus, Parainfluenza virus 1/2/3/4, Human rhinovirus, bocavirus 1/2/3/4, Coronavirus 229E/NL63/OC43, Enterovirus, Metapneumovirus, Respiratory syncytial virus A/B.
[3]*Bordetella pertussis*, *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Streptococcus pneumoniae.*
[4]Rotavirus, Norovirus GI/II, Astrovirus, Enteric adenovirus, Sapovirus.
[5]*Campylobacter* spp., *Clostridium difficile* Toxin B, *Salmonella* spp., *Shigella* spp., Enteroinvasive *Escherichia coli*, *Vibrio* spp., *Yersinia enterocolitica*, *Aeromonas* spp., *Clostridium difficile* hypervirulent, *E. coli* O157, Shiga toxin-producing *E. coli*, Enteropathogenic *E. coli*, Enterotoxigenic *E. coli*, Enteroaggregative *E. coli.*
BUN: Blood urea nitrogen; hs-CRP: High-sensitivity C-reactive protein; HPF: High-power field; IgG: Immunoglobulin G; IgM: Immunoglobulin M; Ab: Antibody; PCR: Polymerase chain reaction.

Complete blood cell counts were as follows: White blood cell count: 7450/μL (segmented neutrophil 32.7%), hemoglobin: 12.0 g/dL, and platelet count: 649000/μL.

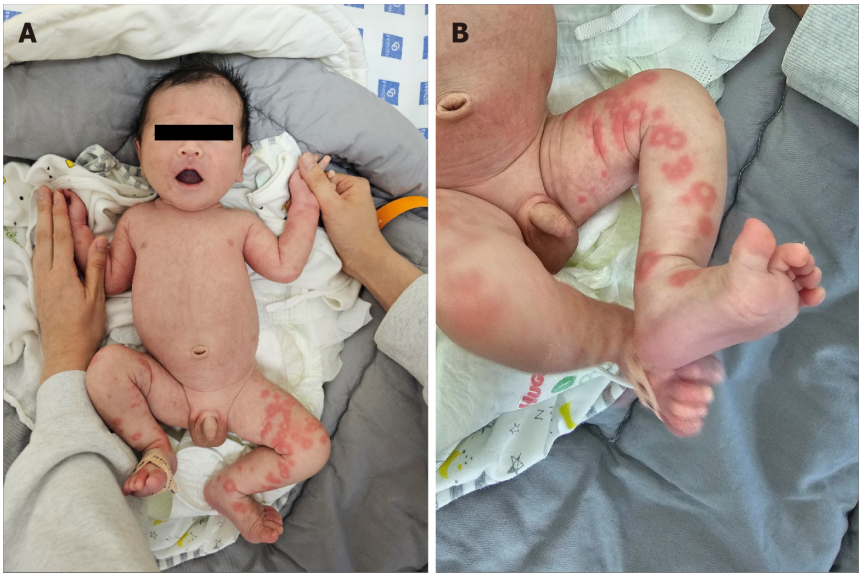

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Figure 1 Neonatal erythema multiforme associated with a rotavirus infection. A: Erythematous papules covering the entire body; B: Annular or target-like lesions are mainly visible on the lower extremities.

Serological tests for Immunoglobulin M for Toxoplasma, Rubella, Cytomegalovirus, Herpes Simplex Virus (HSV), and Epstein-Barr virus viral-capsid antigen were all negative. Multiple polymerase chain reaction (PCR) tests for respiratory viruses and bacterial pathogens on nasopharyngeal swab specimens (including severe acute respiratory syndrome coronavirus 2) were negative (Anyplex II RV16 Detection and Allplex PneumoBacter Assay, Seegene, Seoul, Korea). Based on the possibility of neonatal HSV infection, PCR tests of serum and mucous membrane (conjunctivae, mouth, nasopharynx, and rectum) samples were conducted for HSV-1 and HSV-2, all of which were negative. Multiple PCR tests for gastrointestinal viruses and bacterial pathogens on stool specimens demonstrated evidence of rotavirus infection (Acute Diarrhea Virus and Bacteria Panel, Seoul Clinical Laboratories, Yongin, Korea). No growth was reported in the blood and urine cultures.

FINAL DIAGNOSIS

The patient was diagnosed with EM associated with a rotavirus infection.

TREATMENT

The patient received intravenous fluids for hydration; meanwhile, no other medications were prescribed.

OUTCOME AND FOLLOW-UP

As the neonatal lesions improved rapidly, the patient was discharged on the 3rd day of admission. The patient visited a week later and was noted to be healthy and lesion-free.

DISCUSSION

Various etiologies, including infections, medications, malignancy, and immunization, are responsible for EM[1]. Whilst the disease etiology remains unclear in some cases, infection is a major cause, accounting for up to 90% of all EM cases. HSV is the most commonly identified pathogen in the general population[1]. As neonatal HSV infections are rare but frequently result in negative outcomes, it is highly recognized by pediatricians as a differential diagnosis when skin lesions, not limited to vesicles, are present. However, interestingly, HSV has not been identified as a clear cause of EM in neonates[12-14]. Several infections have been reported to cause EM in neonates, including human parainfluenza virus type 3, cytomegalovirus, and *Pseudomonas aeruginosa*[7,15,16]. However, as some viral infections, such as cytomegalovirus, tend to be asymptomatic, the causal relationship may not be clear, even in the reported cases. Furthermore, vertical or intra-familial (viral) transmission may be considered, including, but not limited to, human papillomavirus

and/or hepatitis-related infections. However, in the current case, as the infant's mother denied any perinatal issue, this possibility seems limited.

Rotavirus is a major cause of gastrointestinal infections in children, including neonates[17]. However, several skin disorder symptoms have resulted from rotavirus infection: Namely, exanthema, Gianotti-Crosti syndrome, and acute infantile hemorrhagic edema[10]. Therefore, even though EM has not been reported following rotavirus infection, the possibility of EM resulting from rotavirus remains. However, scarce gastrointestinal symptoms in the current case leaves room for the question of why such symptoms were not presented. Our patient was directly referred from a postpartum care center (Sanhujoriwon)[18] on the day of admission. A recent study reported a higher prevalence of rotavirus infection among outborn newborns due to such facilities where infections control measures are limited[19]. In hindsight, an association between absolute formula-feeding and rotavirus infection seems highly related. High-impacted studies have shown that formula-fed milk neonates are at higher risk for rotavirus infection[20]. Therefore, it is highly plausible that absolute formula-feeding has contributed to the rotavirus infection, which resulted in EM. Although we present the first case of EM associated with rotavirus infection, it is possible that similar cases may have existed in another similar condition.

As the etiology of EM is unclear, especially in the neonatal period, commonly implemented vaccinations have been assumed to be the cause of neonatal EM, mainly including vaccination against hepatitis B and/or tuberculosis[3-6]. Immunological hypersensitivity reactions to antigens in the vaccine may mediate reactions. As BCG vaccination was not administered in the current case, the possibility of a causal relationship between BCG vaccine and EM is ruled out. Nevertheless, the possibility remains with the hepatitis B vaccine. However, as hepatitis B vaccination is a routine infant immunization administered at birth and recommended globally, it would be nearly impossible to rule out the hepatitis B vaccine as a cause of neonatal EM, including the current case. Conversely, it should be considered that the number of reported cases after the hepatitis B vaccine is very small, considering the doses administered daily, globally.

We believe that this case is important for medical education, as the majority of the literature on neonatal EM does not explicitly identify the disease etiology[13]. Hence, physicians may not initiate testing for all the possible etiologies which may reveal the cause of EM. Furthermore, when counseling the caregivers of patients, physicians may avoid telling patient caregivers that they will be able to identify the cause of the disease. However, as the current case demonstrates, rare and previously unreported causes of the disease could appear with maximal effort. This case may be an example of various diseases with unknown etiologies, implying that physicians should try their best to scrutinize the etiology of the illness.

A limitation of the current case may be that the pathology of the skin biopsy could not be determined. However, as the patient improved rapidly, there was no opportunity or reason to perform a skin biopsy. Similarly, few previous reports on neonatal EM included biopsy findings; we believe that this is a commonly occurring limitation in neonatal management. In addition, the bacterial culture of the stool specimen may have gained bacterial pathogens. However, due to scarce gastrointestinal symptoms culture study of the stool specimen was not conducted.

The current case may not seem severe as the patient improved rapidly without any treatment. However, we believe this case report is important to highlight the novel association between EM and rotavirus and the importance of a comprehensive approach in pathogen identification.

CONCLUSION

Rotaviruses remain a major cause of gastrointestinal infections in neonates and children, therefore, the possibility of rotavirus as a trigger for neonatal EM should be considered.

FOOTNOTES

Author contributions: Kim JJ and Lee JK were the patient's attending physicians; Kim JJ reviewed the literature and contributed to manuscript drafting; Kim JJ and Lee JK were responsible for the revision of the manuscript; all authors issued final approval for the version to be submitted.

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