July 21, 2023

Jin-Lei Wang
Editor-in-Chief
World Journal of Clinical Cases

Re: Ms. No. 85207, Neonatal erythema multiforme associated with a rotavirus infection: a case report

Dear Dr. Wang:

Thank you for the effort and time spent reviewing our submitted manuscript. We would like to thank the reviewers for their pertinent comments. We had a valuable opportunity to improve the original manuscript. The manuscript has been revised based on the reviewers' suggestions and comments.

We sincerely hope that the manuscript is now suitable for publication in the *World Journal of Clinical Cases (WJCC)* and will be pleased to respond to any further queries regarding this submission.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Reviewers' comments:

Reviewer #1: The Neonatal erythema multiforme associated with a rotavirus infection: a case report manuscript's main finding is a neonatal patient with erythema multiforme (EM), whose laboratory diagnostic showed only rotavirus presence, instead of other pathogens which were previously reported to be a cause of EM. The authors assume the majority of the literature on neonatal EM does not explicitly identify the disease's etiology because the physicians do not initiate testing for all the possible etiologies that can cause EM. The authors suggest that clinicians should test for all possible causes of EM to increase the likelihood of identifying the causative agent. While I agree with this suggestion, I believe that extended testing should only be conducted if it has meaningful clinical relevance, such as applying a specific treatment for the causing agent. In this case, there is no specific medication to treat Rotavirus infection besides treating the symptoms, and the symptoms of EM improved rapidly without further medication.

Response: We sincerely appreciate the careful evaluation of our manuscript and the constructive comments. We recognize that, in the current case, there was no specific medication to treat rotavirus infection besides treating the symptoms. At the initial encounter, however, as the diagnosis of rotavirus infection was not established, treatable diseases including, but not limited to, bacteremia or neonatal sepsis (which have meaningful clinical relevance) were also considered as possible etiologies. Nevertheless, as the reviewer has pointed out, in the current case; actually, no active treatment was carried out. Therefore, we emphasized the possible causable relationship between rotavirus infection and EM.

Additionally, the study's limitation is that it associates the presence of Rotavirus amino acid in the blood with EM, which may be a correlation rather than causation. Further examination is needed to confirm that Rotavirus causes EM.

Response: We apologize for the confusion that has been caused. In general, as the rotavirus infection is diagnosed via its presence in the stool via polymerase chain reaction (or immune-based assays), we have also used stool specimens for the detection of rotavirus (mRT-PCR) (*J Clin Microbiol*. 2011;49(5):1926.). Therefore, we have stated that the specimen that was positive for rotavirus was stool. Furthermore, we have also found that the specimens tested for respiratory viruses and bacterial pathogens were also not properly designated. We have also added additional descriptions for the respiratory specimens. The corrections were also applied

to Table 1. We believe that further reports following the current study may intensify the possible causal relationship between rotavirus infection and EM.

In the revised manuscript:

"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."

"Multiple 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)."

1 Title. Yes, the title perfectly reflects the main subject of the manuscript.

2 Abstract. Yes, the abstract summarizes the manuscript.

3 Key Words. Yes, the keywords highlight the topic of the manuscript.

4 Background. Overall yes, but the authors should consider complementing the introduction with more extensive information about rotavirus vaccination. Furthermore, the authors should deliberate to add more references about cutaneous disorders implicated by rotavirus.

Response: We appreciate the constructive and thoughtful comment. We have added additional comments based on the Reviewer's recommendations. Additional references were cited for the added statements.

In the revised manuscript:

"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

[2], 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."

5 Methods. The serological tests for several viral IgM and the multiplex PCR-based detection of bacterial and viral infections are adequate methods to uncover acute bacterial or viral infections. However, after the positive rotavirus PCR results, I would have recommended stool-based rotavirus detection as confirmation of acute rotavirus infection.

Response: Thank you for the positive evaluation of the tests we used to uncover acute bacterial or viral infections. As stated in the previous response, the positive rotavirus PCR result was gained from the stool specimen. We have made corrections to ensure the manuscript and the Table are clear.

In the revised manuscript:

"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."

6 Results. The laboratory results for infection detection are interpreted clearly. A skin biopsy could be a validation for the EM diagnosis but it was not performed because of the rapid improvement of the EM and the youngness of the patient. In my opinion, other detection methods for acute rotavirus infection such as stool culture would have supported the association between the rotavirus infection and the EM.

Response: We also regret that we could not acquire a skin specimen; however, we think this was favorable for the infant, as the symptoms did not exacerbate. We agree that stool culture would have supported the association. Regrettably, culture for rotavirus nor other bacterial pathogens was not performed, despite multiple PCR for bacterial/viral pathogens performed on stool specimens. Referentially, cell culture for rotavirus is usually not used routinely for clinical diagnosis due to its laborious technique (*J Clin Microbiol*. 1983;18(2):310.). We have stated this limitation in the Discussions.

Added in the revised manuscript:

"In addition, bacterial culture of the stool specimen may have gained bacterial pathogen. However, due to scarce gastrointestinal symptoms culture study of the stool specimen was not conducted."

7 Discussion. The manuscript interprets the diagnosis and the laboratory findings. The findings' relevance to the literature could be explained better with additional examples of skin disorder symptoms caused by rotavirus infection. Rotavirus has been rarely implicated with some cutaneous disorders such as generalized maculopapular exanthema, infantile acute hemorrhagic edema, Gianotti-Crosti syndrome, and macular exanthema. Furthermore, in most of the cases when rotavirus caused skin disorders there were classical gastrointestinal symptoms also such as fever, diarrhea, vomiting, and dehydration. However several articles demonstrated that neonatal EM developed following hepatitis B vaccination (e.g. doi: 10.5021/ad.2011.23.3.382 and 10.1016/j.pedneo.2015.03.012). The authors mentioned that the patient was vaccinated with the first dose of hepatitis B on the day of birth. Considering these facts, I`m not convinced that there is a causation between the rotavirus presence without classic gastrointestinal symptoms and EM, or it is just a correlation.

Response: Based on the Reviewer's comment, we have added descriptions regarding skin disorder symptoms caused by rotavirus infection. We believe the Reviewer's doubt on the causation between the rotavirus presence without classic gastrointestinal symptoms, and EM is reasonable. Therefore, we have discussed the possibility of EM associated with hepatitis B vaccination. As stated in the manuscript, not limited to the current case, as hepatitis B vaccination is administered to nearly all newborns globally, it would be difficult to rule out hepatitis B vaccination as a cause of neonatal EM. Conversely, considering the number of hepatitis B vaccinations administered at birth, it might be reasonable to think that the number of reported EM is somewhat too small. Based on the Reviewer's instructive concerns, we have added a separate paragraph to discuss this issue in the Discussion section.

In the revised manuscript:

"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."

Added in the revised manuscript:

"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."

8 Illustrations and tables. Overall yes, Table 1. is clear and informative. I would recommend adding the clinically normal range to Table 1. The demonstration of neonatal EM on Figure 1. Is clear and representative.

Response: Thank you for the comment. Reference intervals have been added based on the age-specific values based on Reference Intervals for Laboratory Tests and Procedures in the *Nelson Textbook of Pediatrics*, Chapter 748, e5-e14. Note that certain values are age-specific and different from those of adults.

9 Biostatistics. There was no biostatistics in the article.

10 Units. Yes.

11 References. References are appropriate.

12 Quality of manuscript organization and presentation. The manuscript is overall clear, well-organized, and grammatically correct.

13 Research methods and reporting The manuscript was prepared according to the standards for case reports.

14 Ethics statements. The uploaded documents contain the consent for treatment form.

We appreciate the constructive and encouraging comments.

Reviewer #2: Response to Authors, In this case report, Kim et al. and colleagues reported that neonatal erythema multiforme (EM) is associated with a rotavirus infection. Even if the case report seems interesting for observing the clinical rareness of neonatal EM due to rotavirus infection, I have a few concerns about the clinical scenarios and strategies.

Response: Thank you for the positive evaluation of the manuscript. We have attentively made corrections based on the Reviewer's comprehensive comments.

1. As previously, high-impacted studies have shown that formula-fed milk neonates are at higher risk for Rotavirus infection[1]. Henceforth, is it definitive that rotavirus infection was related to formula fed-milk other than EM? How did the physicians rule out this important scenario? Could you please elaborate on this specific issue? (1) J Hosp Infect. 1984;5(4):438-443, PMID: 6085100

Response: We appreciate this insightful comment, in specific. Based on the Reviewer's comment, we have added additional statements on the high risk of acquiring rotavirus infection in the current case with the reference the Reviewer has provided. We believe that the scenario that the Reviewer has proposed is considerably reasonable.

Added in the revised manuscript:

"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."

2. Did the authors think of the possibility of other triggering factors for EM, such as hepatitis B and BCG vaccination in infants? And if did, then how did the physician rule it out? Please explain. In addition, did the neonate have had BCG immunization? To date, there have been two reports suggesting an association of EM with BCG vaccination as a nonspecific reaction[2,3]. These reactions may be mediated by immunological hypersensitivity reactions to antigens in the vaccine. Hence, the authors need to point out the BCG vaccination history too, it can be shortly discussed. (2) S Afr Med J. 1980;57:332–334, PMID: 7355353 (3) Arch Dermatol. 1979;115:614–615, PMID: 443840

Response: In the current case, BCG vaccination was not administered. We have discussed the issue in the Discussions and have cited the references provided by the reviewer. Thank you for the comment.

Added in the revised manuscript:

"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.

3. Do the parents have a history of any HPV and/or hepatitis-related infections, specifically the mother of the neonate? If not, the authors need to briefly discuss, and clearly mention this differential diagnosis history in the case report.

Response: Thank you for pointing out other causes of the skin presentation. We have added additional statements on the raised issue after asking additional inquires. We also have shortly discussed the differential diagnosis in the Discussions.

Added in the manuscript:

"Paternal and maternal history of human papillomavirus and/or hepatitis-related infections was denied."

"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."

We sincerely appreciate the instructive comments.