Author's response to reviews

Title: Measles Infection Causing Bacillus Calmette-Guérin Reactivation: A Case Report

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The Editor

BMC Pediatrics,

Please find enclosed our revised manuscript on Measles Infection Causing Bacillus Calmette-Guérin Reactivation: A Case Report.

We have included all our responses to the reviewers’ comments and descriptions of the manuscript changes, below:

Reviewer 1

Reviewer’s general comments

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Author’s response

We thank Reviewer 1 for the important and useful comments on the manuscript. We have addressed all the specific comments as indicated in the table below.

Specific comments:

1. Well written case report, though it might be a bit too long. The text could be shortened which would make it more likely to be read. E.g. the description and discussion of KD could be shortened without losing any information We thank the reviewer for the feedback.

We have shortened the text, including the discussion on KD as suggested (Lines 189-190)
2. I would have liked to have had a description of the BCG-scar from before the actual measles-infection. Had it healed completely? If available please add to the text.

The BCG scar had healed completely before the measles infection. This has been added to the test. (Lines 99-90)

3. I cannot access ref 10. Wrong address?

We apologize, as the web link was no longer available. This has been corrected. (Lines 384-386)

Reviewer 2

Reviewer’s general comment

Thank you for an interesting manuscript that provides a new case-report of a seemingly novel discovery - that measles infection can lead to "reactivation" of BCG. I have some major and minor comments/edits to suggest.

Author’s response

We thank Reviewer 2 for the positive feedback and important comments. We have addressed all the specific comments as indicated in the table below.
Specific comments:

1. First, I believe that it would be better for the overall readability and comprehensibility of the manuscript if the photo of the BCG reaction is displayed earlier.

We agree with the reviewer, and the image should be displayed earlier in the finished publication.

2. Also, I would prefer if the authors could describe in closer detail how the reaction actually looked. The pictures I received were in a low resolution, but to me it seemed that the BCG reaction had not transformed into a BCG scar yet before the measles infection. This is, however, just guessing on my side, but upon interview with the parents it should be possible to retrieve detailed information to confirm whether the reaction was, in fact, a pustule before the infant was infected with measles. The standard BCG reaction route is: No reaction for 2-4 weeks -> Papule for 1-2 months -> Pustule during 3-6 months -> Scar I interpret having a BCG pustule as having live-attenuated bacteria still present at the site of vaccination with the pus discharge thus being a mixture of dead mycobacteria and neutrophils. If the infant had a BCG pustule at the time it was infected with measles, then what the authors are presenting is in fact a reactivation of BCG, given that the immunocompromised status of the infant allowed BCG to start replicating to larger numbers and thus produce the induration, redness and probably pain at the site of original inoculation. If the infant had completed the normal course of BCG reactions by 7 months of age and thus had a scar, then it is less likely that viable mycobacteria were still present at the site of the inoculation, and the BCG "reactivation" (induration and redness seen) would be more likely to be a non-specific activation of immune cells located at the inoculation site with an absence of mycobacteria. It would thus technically not be a reactivation. Since that measles disease diminishes the immune response, I believe it is most likely that the infant had a pustule or a semi-healed BCG scar than a completely sealed BCG scar and I would appreciate the author's considerations on this point in the article.

I would appreciate considerations from the authors as to whether they believe that BCG "reactivation" represents reactivation of BCG mycobacteria which most thus still be present at the inoculation site or a non-specific stimulus of the immune system due to induction of cytokines and inflammatory responses caused by measles.
We thank the reviewer for these important points, which we had neglected to include in the initial manuscript.

The BCG had in fact healed completely and formed a scar. This has been added to the text to make it clearer. (Lines 88-90, 106)

As the BCG had healed completely before the onset of the measles infection, we believe the reactivation of the BCG was more likely to be due to an immune mediated process, rather than to the multiplication of live Mycobacterium bovis BCG at the BCG scar site.

Although the reactivation and multiplication of live but dormant bacilli is a possibility in this case, other characteristics/features of the case seem to suggest that the reactivation of the BCG was more likely due to an immune mediated process (and possibly similar in mechanism to those hypothesized in the BCG reactivation seen in children with Kawasaki disease). These characteristics/features have been added to the discussion, and include:

a. The rapid onset and resolution of the BCG site erythema/induration with the appearance and resolution of the measles rash. Immune suppression induced by measles would normally be expected to persist for a longer duration.

b. The lack of malnutrition in the patient

c. The otherwise uncomplicated measles course

d. The absence of secondary infections normally seen in severe immunosuppressed states.

(Lines 255-271)

3. An explanation of the normal sequence of BCG reactions in the beginning of the manuscript would also ease the understanding of this.

This has been added to the Introduction (Lines 49-52)
4. If possible, it would be appreciated to include which strain of BCG that the infant had received and whether the infant was vaccinated at a health center or a major hospital. BCG strains are known to contain different colony-forming units (CFUs). A major determinant for the development of BCG pustules and BCG scar reaction rates is the strain of BCG administered. Also, the size of the post-vaccination wheal is important. It is thus probable that infants that received a vaccine containing more CFUs and a high vaccine dose (as measured by the post-vaccination wheal) are more likely to have a BCG pustule (containing live-attenuated BCG) for a longer time. If possible to retrieve these data from the child's vaccination card or national data concerning the BCG strains used in the country, it would be a good addition to the article. Infants vaccinated at major health centers are more likely to have been vaccinated by an experienced vaccinator.

We thank the reviewer for highlighting these points. The information has been added to the manuscript. (Lines 87-90)

5. The discussion features a rather long description of standardized diagnostic procedures in measles infections. This section does not fit well in the discussion section.

The section has been removed from the discussion. (Lines 174-178)

6. There is some mentioning of the possibility that this infant could have suffered other viral infections as well, aside from measles infection, and that any such infection could be responsibility of the induration at the inoculation site, rather than measles. This is a good point and also a weakness of the study since the infant was not tested broadly and it should be stated clearer that it is unknown whether the "reactivation" occurred due to the measles infection or due to another infection. Theoretically, for example, the infant could have suffered from acute-HIV+measles and thus was immunocompromised which gave the still-live mycobacteria at the inoculation site the possibility to replicate.

We agree that this is a weakness of the current study. We have re-written the sentence to state more clearly that it is unknown whether the "reactivation" occurred due to the measles infection or possibly due to a co-infection with other pathogens. (Lines 244-246)
7. I request also further details on the diagnostic workup of coronary artery disease in Kawasaki's disease so that it is clear whether the two echocardiographic examinations performed are sufficient to rule out any heart conditions in this infant.

This echocardiography work-up is usually appropriate to detect and rule out coronary involvement in children with Kawasaki disease, as suggested by most guidelines. (Eleftheriou D, Levin M, Shingadia D, et al. Arch Dis Child 2014;99:74-83)

8. Finally, it should be stated which databases were sought to identify other cases of "BCG reactivation" during acute measles infection. It was both unclear which databases had been sought and which search words or MeSH terms that the authors applied. "To our knowledge" is insufficient.

We thank the reviewer for highlighting this point. PubMed/MEDLINE database was searched for published literature of similar cases using the search terms “Bacillus Calmette-Guérin”, “Bacille Calmette-Guérin”, “BCG” and “measles”. This has been added to the text. (Lines 143-145)

9. I attach a PDF with some minor edits and suggestions to the manuscript, which I would be happy to review again after the above input has been processed.

We thank the reviewer for the suggestions on these minor edits. These have been included in the revision. (Lines 45,59,64,92,116,126,155-174,279,306)

We have uploaded the revised manuscript with tract changes, with this submission.

Thank you.

Sincerely,

Anand Mohan