Author’s response to reviews

Title: A Neonate with Left Pulmonary Artery Thrombosis and Left Lung Hypoplasia: A Case Report

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Author’s response to reviews: see over
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To:

Professor Michael Kidd, AM

Editor-in-Chief, Journal of Medical Case Reports

Executive Dean
Flinders University
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Adelaide, Australia

Dear Dr. Kidd:

My colleagues and I are re-submitting to the Journal of Medical Case Reports a revised manuscript of the case report entitled A Neonate with Left Pulmonary Artery Thrombosis and Left Lung hypoplasia to be considered for publication as a neonatal case presentation.

We clarified below in red characters our response to the different suggestions of the reviewers. Appropriate changes have been completed and tracked in blue characters within the body of the article.

The manuscript is being submitted only to Journal of Medical Case Reports and will not be submitted elsewhere while under consideration. All authors have participated in the concept and design, drafting or revising of the manuscript, and they have approved the manuscript as submitted. In addition, the authors do not have any affiliation or financial agreement with any company.

Reviewer 1:

Comments to authors:
This is a case report of an infant with spontaneous pulmonary artery thrombosis resulting in pulmonary hypoplasia.
The report is very well written and informative however there are a few additional points that need clarification:
1. Family history of spontaneous thrombosis: There is no family history of spontaneous thrombosis (this statement was included in the case report section)

2. Since the maternal history was significant for 2 previous abortions, was the mother tested for lupus anticoagulant and anticardiolipin antibody? Was a homocysteine level obtained?: Mother was encouraged to follow up with her physician and pursue the possibility of an inherited thrombophilia disorder. Since the thrombophilia evaluation on this neonate was within normal, the mother did not pursue
further thrombophilia work up. The following statement was included in the case report. The mother did not complete a thrombophilia screening evaluation.

3. Since this is a case of spontaneous arterial thrombosis an extensive work up is warranted including levels of plasminogen, lipoprotein(a), homocysteine and Methylene tetrahydrofolate reductase (MTHFR). The following thrombophilia evaluation was completed on this infant (this statement was included in the case report): A screening evaluation for a possible thrombophilia disorder was completed in this infant. Blood levels for protein C, protein S, antithrombin activity, concentration of clottable fibrinogen, plasminogen activity, activities of coagulation factors VIIIC and XII, lipoprotein (a) and homocysteine concentration were within normal. In addition, DNA-based assays (ie, factor V G1691A mutation and factor II G20210A variant) were also normal.

A DNA based assay for evaluation of a possible Methylene tetrahydrofolate reductase deficiency (ie, MTHFR C677T genotype) was not completed since homocysteine level in this neonate was within normal.

4. Being placed on ECMO it should be clarified that the infant was heparinized. In addition, if anticoagulation was not continued post-ECMO because of thrombus resolution by echocardiogram this needs to be mentioned. This infant was heparinized during his ECMO course (this statement was included in the case report). We have previously stated in our case report the following: “since the management of arterial thrombosis in the neonatal period is controversial, no further anticoagulant therapy was administered post-ECMO”.

5. Since the infant was followed until 18 months of age it is worth reporting on his pulmonary outcome: any pulmonary sequelae? Reactive airway disease? Frequent hospitalizations? This infant was closely followed up till 18 months of age. He did not require further hospitalization post his NICU discharge nor suffered from reactive airway disease (This information was included in the case report).

The discussion section is brief and to the point, however it is suggested to add the following:
1. Brief discussion of thrombotic risk factors in newborns
2. Discussion on possibility of MTHFR deficiency

We previously stated that “Neonatal arterial thrombosis is in most cases iatrogenic from indwelling arterial catheters or lines and is rarely described at birth”. We also clarified that congenital thrombophilia (including MTHFR deficiency) could also placed a neonate at high risk for thrombosis (This information was included in the case report). The following reference was also added. Veldman A, Marcel FN, Michel-Behnke I. Thrombosis in the critically ill neonate: incidence, diagnosis and management. Vascular Health and Risk Management 2008: 4(6): 1337-1348.
Reviewer 2:

Comments to authors:

The timing of the studies in the first portion of the (echocardiogram and CTA) should be explicitly stated (ie ** hours postnatally). The echocardiogram and CTA were performed at 10 and 16 hours of life respectively (this information was included in the case report).

The authors state that aortopulmonary collaterals were seen to supply the L lung in their discussion. It would be helpful to include an image showing this after Figure 3. This figure was included.

The authors did not include the following case report which describes a similar event to the one in this manuscript. As such the introduction and abstract should be altered to include this earlier report:
Lytrivi I, Reingold S, Ramaswamy P. Pediatr Cardiol. 2008 Sep;29(5):1002-3. Neonatal left pulmonary artery occlusion and postinfarction cysts of the left lung: cause and effect? This case report was included in the introduction, abstract and references.

Reviewer 3:

Comments to authors:

The authors report a case in which there was left lung hypoplasia and a left pulmonary artery thrombosis; they postulate that an intrauterine insult occurred between the fifth and eight weeks of gestation.

Comments:
1. If a thrombosis had occurred at 5-8 weeks of gestation it seems unlikely that the thrombosis would still be present some 30 weeks later. Other articles such as reference # 12 have also postulated that this vascular event could have occurred very early in fetal life.

2. Idiopathic unilateral pulmonary hypoplasia does occur. An alternative explanation for the findings is there was abnormal pulmonary vasculature associated with abnormal lung development and at some point late in gestation a thrombin formed. This could be another possible scenario and was included in the discussion section.

3. The authors do not present the results of antithromin, protein C, protein S or factor V Leiden levels. Nor indeed if these were repeated as levels taken in the neonatal period are difficult to interpret. What are the authors’ lab’s normal ranges? The vitamin K dependent inhibitors of coagulation, protein C and protein S and antithrombin can be reduced in the neonatal age group and thus sometimes difficult to interpret. However, the levels in this neonate were within normal and thus were not repeated after 6 months of life. Evaluation for Factor V Leiden deficiency is a DNA based assay and should not be affected by age and thus is typically performed at birth.
(see reference # 10). The normal range for these factors is as follows at Arkansas Children’s Hospital. Antithrombin III: 39-87%; Protein S total: 12-60%; Protein C total: 17-64%.

4. Much of the report of the course of the case could be omitted.

5. In the discussion the authors state congenital pulmonary hypoplasia occurs when any or a combination of factors is absent or impaired. Unilateral pulmonary hypoplasia has other explanations or may be idiopathic. We clarified in the introduction and discussion that congenital pulmonary hypoplasia could be idiopathic.

We look forward to your response and comments.

Sincerely yours,

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