1. The authors mention in the Summary that "However, the use of DMARDs during pregnancy may pose potential risks to the fetus." “Her serologic laboratory results, including rheumatoid factor, anti-cyclic citrullinated peptide antibody, and anti-nuclear antibody, were negative.” in the Case presentation. The question is whether the patient was on disease-modifying antirheumatic drugs (DMARDs)? And the resulting risk to the fetus? Please explain.

->Answer: Thank you for your thoughtful comments. In the treatment of immune-related conditions like AOSD, where drugs such as cyclosporin and tacrolimus are commonly used. However, information regarding potential risks during pregnancy associated with the use of these medications must always be considered. Current data does not suggest an increased risk of major congenital malformations following fetal exposure to cyclosporin or tacrolimus. However, there have been reports of increased risks of low birth weight and preterm birth, likely attributable to maternal conditions rather than direct medication effects. Based on this evidence, experts may consider the use of cyclosporin or tacrolimus during pregnancy to be permissible. Nevertheless, using the term "immunosuppressants" when providing such information could be clearer and reduce confusion. While the term "DMARDs" (Disease-Modifying Anti-Rheumatic Drugs) is sometimes used, it encompasses a broader range of anti-inflammatory medications and may not sufficiently clarify when used during pregnancy. Therefore, using the term "immunosuppressants" helps ensure that specialists have a clear understanding of the clinical context and can provide unambiguous information to stakeholders.

“The management of AOSD during pregnancy involves utilizing NSAIDs, glucocorticoids, and, in severe cases, immunosuppressives, despite potential fetal risks such as low birth
weight and preterm birth, highlighting the delicate balance required in addressing the complexities of AOSD during gestation.”

2. “The risk of heredity in AOSD is not well-defined, but it is likely that the disease is multifactorial, with both genetic and environmental factors contributing to its development. Therefore, the risk of heredity may be influenced by the genetic background of the patient, as well as environmental factors such as infections and stress.” Could this case provide clinical data to support this section?

->Answer: I respect your reasonable suggestion. I added some explanation as follows:

“This case serves as evidence that the intricate interplay of genetic predisposition, the unique circumstances of pregnancy in a mother with AOSD, and various environmental factors can collectively contribute to the development of neonatal HLH. The underlying genetic background of AOSD in the mother, compounded by the physiological changes of pregnancy, may have influenced the fetal environment, potentially predisposing the newborn to HLH. Moreover, the management of AOSD during pregnancy, including the use of medications like glucocorticoids and immunosuppressive agents, could have further influenced the fetal immune response. Additionally, environmental factors such as infections and stressors during pregnancy may have exacerbated the risk of HLH development in the newborn. Overall, this case underscores the complex nature of disease pathogenesis, highlighting the need for comprehensive understanding and management of both genetic and environmental factors in similar clinical scenarios.”

3. In the article, the authors did not mention the basis on which the infant met the diagnostic criteria for HLH or whether genetic testing was performed on the infant? Please add this
Answer: According to modified 2009 diagnostic criteria of familial HLH (Ref 1), the male infant was satisfied with 7 parameters including fever, splenomegaly, anemia and thrombocytopenia, hypofibrinogenemia, hyperferritinemia, elevated soluble IL-2 receptor, and evidence of phagocytosis on bone marrow biopsy. As you recommended, this section was added in revised manuscript.
