Dear Reviewers,

On behalf of my co-authors, we thank you very much for the reviewers' comments concerning our manuscript entitled "Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report" (Manuscript NO. 61494, Case Report). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied all the comments carefully and have tried our best to make the correction. There are still a few problems in our study that can not be solved at present. We will continue to pay attention to them in further researches according to your suggestion.

The main corrections in the paper and the responses to the reviewer's comments are as follows:

Reviewer #1:

1. The most important limitation is that the authors completely disregarded the potential pathogenic role of high-grade systemic inflammation and fever present in the patient at the moment of LQTS/TdP.

Response: This is a very important point. We agree with this concern. Recent findings have demonstrated the key roles of systemic inflammatory activation and fever in promoting long-QT syndrome (LQTS) and TdP development. Studies have demonstrated that induction of inflammatory cytokines can directly cause the dysfunctions of several cardiac ion channels. Besides these direct effects, systemic inflammation might also indirectly favor LQTS/TdP-axis by several additional mechanisms, including the induction of episodic fever and related temperature-mediated changes in cardiac ion channels' biophysical properties. We have highlighted all these aspect and carefully discussed in **paragraph 5 of Discussion section**, and added all related references in the manuscript.

2. Based on the above consideration, it is important that the authors provide more detailed information regarding the extent of the systemic inflammatory activation in this patients. In particular, they reported that C-reactive protein (CRP) levels were markedly elevated at the initial laboratory test (>160 mg/L), but no data are provided regarding CRP when TdP occurred (even if the concomitant presence of high fever and chill strongly suggests that systemic inflammatory activation was elevated). In this regard, if available, additional information on cytokine blood levels (particularly IL-6) may be very insightful.

Response: Thanks for your professional advices. Unfortunately, cytokine levels were not measured in this case; however, significantly elevated CRP levels reflected systemic inflammatory activation. CRP level remained extremely high (>160 mg/L) when TdP occurred. We have added this information in **Final diagnosis section**.

3. Accordingly, the title should be changed from "Torsades de pointes episode in a female with high-grade fever: A case report" to "Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report". Moreover the potential role of the inflammatory activation and fever should be highlited also in the Abstract.

Response: We have changed the title to "Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report". In the Abstract, we highlighted the potential role of the inflammatory activation and fever.

4. The presence of other concomitant risk factors probably favoring TdP should be also more accurately discussed. In fact, multiple concomitant risk factors are usually necessary for TdP occurrence, as normal action potential duration in ventricles is preserved by numerous often-redundant ion channel

mechanisms. Please expand this aspect in the discussion at the light of the above fundamental references.

Response: We have expand this aspect in **the last paragraph of Discussion section** and added related references.

5. Genetics: the authors reported that the patient (and her father) had heterozygous mutations of KCNH2 (c.1370C>T) and AKAP9 (c.7725A>C). Are these specific mutations already descrive in the literature as pathogenic for LQTS?

Response: LQT1 (KCNQ1, 30%-35%), LQT2 (KCNH2, 20%-25%), and LQT3 (SCN5A, 5%-10%) represent most of the genotype-positive cases. KCNH2 mutations produce defective hERG protein, resulting in a decrease in IKr activity. AKAP9 mutations with low frequency (<1%) disrupt its interaction with KCNQ1, reducing cAMP-stimulated phosphorylation of KCNQ1 and abolishing IKs upregulation. We haven't yet read the literature about the specific mutations of KCNH2 (c.1370C>T) and AKAP9 (c.7725A>C) we reported in this case, and we will continue to pay attention to this.

6. In the discussion, the authors correctly stated that "The difference in the sex hormones is considered to be the main reason for this gender difference of lethal arrhythmias. It is now becoming clear that sex hormones play an important role in cardiac repolarization and the control of QT intervals". Please provide specific key references to substantiate this statement.

Response: We supplemented specific key references to substantiate this statement.

7. At the beginning of the discussion, the authors stated that "Here, we present a case of AOSD showing TdP accompanied with long QTc". In order to better reflect the pathogenic sequence of the events, please change to "Here, we present a case of AOSD showing long QTc complicated with TdP".

Response: At the beginning of the discussion, we have revised the statement to “Here, we present a case of AOSD showing long QTc complicated with TdP”.

Reviewer #2:

1. The manuscript was not typed based on Baishideng criteria.

Response: We have adapted the manuscript based on Baishideng criteria.

2. Laboratory examination - the authors mentioned "Cervical lymph node biopsy revealed T cell significant proliferation. Bone marrow biopsy indicated infectious imaging". Please add the pathologist in the authors team and add a detailed description of the lymph node and bone marrow, with relevant figures.

Response: Cervical lymph node biopsy indicated symptoms of lymphocytic hyperplasia. The follow-up immunohistochemical analysis revealed that lymphocytic proliferation was mainly due to the T cell proliferation. Bone marrow puncture indicated that the proliferation of granulocytes was significantly active, and the proportions of intermediate and advanced granulocyte stages were significantly increased. Cellular morphology analysis suggested infection-associated reactive hyperplasia of the granulosa. We added this detailed description in **Laboratory examinations section** and the relevant reports and figures in **Supplementary Material**. The pathologists are also listed in the authors team.

3. In Introduction, diagnostic criteria for Still disease need to be presented, to can sustain the present case. Please move the diagnostic criteria from Discussion to Introduction.

Response: Thanks for your suggestion. We have moved the diagnostic criteria for Still disease from Discussion to Introduction.

4. Can be Still disease reversible?

Response: AOSD is a systemic inflammatory disorder presenting daily abruptly spiking fevers, leukocytosis, evanescent rash, and arthritis. Analysing AOSD disease course, 3 different clinical patterns of AOSD have been identified: i. monocyclic pattern, characterised by a systemic single episode; ii. polycyclic pattern, characterised by multiple, ≤ 1 year lasting, flares, alternating with remissions; iii. chronic pattern, related to a persistently active disease with associated polyarthritis. A large percentage of patients experiences several flares with an evolution toward the chronic disease course and up to 16% of patients die during the follow up, due to AOSD-related complications [Reference: Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun 2018; 93: 24-36. PMID: 30077425 DOI: 10.1016/j.jaut.2018.07.018].

5. Treatment - the authors mentioned "The genetic analysis verified the patient and her father with QTc interval of 490 ms had heterozygous mutations of KCNH2 (c.1370C>T) and AKAP9 (c.7725A>C) while her mother had normal QTc interval and had no mutations ". Please add technical data. How these mutations were detected? Which technique was used for detection?

Response: Peripheral blood samples were collected from the patient, her mother, and her father. Total genomic DNA was extracted from peripheral blood samples of all subjects using a blood DNA extraction kit (TIANGEN, Beijing, China). Targeted gene capture sequencing was performed by MyGenostics (Beijing, China). Briefly, biotinylated capture probes were designed for the exons of 74 genes related to the cardiovascular system, and then the sequencing was performed using Illumina HiSeq 2000 Next-Generation Sequencing platform, and the sequencing data were analyzed by professional bioinformatics analyst (MyGenostics, Beijing, China). We added these technical data in **Treatment section**.

6. If the authors chose to discuss the gene profile, this part should be significantly enlarged. In Discussion, please add more literature data regarding these gene profile. Which might be the evolution of the case? It is indeed congenital/ Please argue....

Response: This is a very important point. We have enlarged this part and updated literature data in **paragraph 6 of Discussion section.** Based on the clinical manifestation and examinations, we conclude that TdP with long QTc, in this case, could be associated with the patient's genetic background and the acquired triggering effects from sex, antibiotics, high-grade systemic inflammation, and fever.

We appreciate for Editors/Reviewers' warm work earnestly and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.