Dear Editor,

Thank you for your comments and concerns regarding our manuscript (number: 69817) titled "Tuberculosis-associated hemophagocytic lymphohistiocytosis misdiagnosed as systemic lupus erythematosus: a case report and literature review." We have received comments on our manuscript and have reviewed them carefully. Our point-by-point responses to these comments are provided below.

**Reviewer 1**

**Comment 1:** I think this manuscript needs meticulous revision of platelet number throughout. I think this manuscript needs meticulous revision of platelet number throughout. The patients platelets were platelets $64*10^9$/L, only at the regional hospital before admission to the authors' hospital. Since then the counts mentioned in the manuscript are: Page 6: Laboratory tests showed anemia (red blood cell (RBC) count $3.11*10^{12}$/L, hemoglobin (HGB) 89 g/L, WBC count $2.59*10^9$/L, neutrophil (NEU) count $2.13*10^9$/L, PLT count $276*10^9$/L), and routine urine tests demonstrated protein (++) and proteinuria (1.15 g/24 h). Page 9: PLT count $264*10^9$/L. Page 9: PLT count $199*10^9$/L Page 9: PLT count $293*10^9$/L Page 10: According to the HLH-2004 criteria, given the presence of cytopenia (Hb <90 g/L; platelet <100 × $10^9$/L; 2 out of 3 lineages), or else it is only one cell lineage. Page 10: According to the HLH-2004 criteria, given the presence of cytopenia (Hb <90 g/L; platelet <100 × $10^9$/L; 2 out of 3 lineages), or else it is only one cell

lineage. Page 11: Y (hemoglobin 53 g/L, platelets 64*$10^9$/L) (Table 2) The HLH score has to be revised.

**Response:** Thank you for your valuable advice. We apologize for not clearly stating the patient' s history. The patient underwent platelet transfusion many times at local hospitals before presenting to our hospital except antibiotics and granulocyte colony-stimulating factor (G-CSF). `We think this may be the reason why laboratory tests showed anemia (red blood cell (RBC) count 3.11*$10^{12}$/L, hemoglobin (HGB) 89 g/L, WBC count 2.59*$10^9$/L, neutrophil (NEU) count 2.13*$10^9$/L, PLT count 276*$10^9$/L) (Page 6). SLE was suspected, and methylprednisolone was given. Methylprednisolone produces a significant rise in platelet count (1-3), which we think can explain the following results: PLT count 264*$10^9$/L, PLT count 199*$10^9$/L PLT count 293*$10^9$/L. Therefore, we believe that the PLT count was decreased before treatment. According to the HLH-2004 criteria, there are two cell lineages. In Table 2, cytopenia=2 cell lines in peripheral blood (hemoglobin 53 g/L, platelets 64*$10^9$/L). In Table 3, there were 2 lineages involved in cytopenia.

**Comment 2:** Relative weights of the additive classification criteria items (positive ANA was the entry criterion). The patient' s SLE classification score was 26 according to the 2019 EULAR/ACR classification criteria. SLE can be diagnosed based on a score of 10 or more if the entry criterion is fulfilled. From table 1 score is 29, without thrombocytopenia, score is 25.

**Response:** Thank you for your valuable and insightful comments. According to the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus (4), within each domain, only the highest weighted criterion is counted toward the total score. Leukopenia (relative weight: 3) and thrombocytopenia (relative weight: 4) both belong to the hematological domain. Only thrombocytopenia was counted toward the total score. Therefore, the patient' s SLE classification score was 26, without thrombocytopenia, and the score was 25 according to the 2019 EULAR/ACR classification criteria.

**Comment 3:** Page 9: Fifteen days after discharge, the patient was readmitted with fever. (kindly mention how much) Page 9: Methylprednisolone (24 mg QD po) and hydroxychloroquine sulfate (200 mg BID po) were started. After 2 days, the patient felt much better, her fever subsided, and her appetite improved. Page 9: We adjusted the treatment plan to intravenous methylprednisolone (40 mg/day QD) for 1 day. Page 9: We increased the dosage of methylprednisolone (80 mg/day QD) again Despite the afore-mentioned steroid therapy, the authors did not count known immunosuppression in the HScore for HLH, which adds 18 points to the score.

**Response:** Thank you for your valuable advice. Regarding the HScore for HLH, we apologize that we neglected to state thatsteroid therapy can lead to

immunosuppression. As such, the HScore should increase by 18, and the patient thus had an HScore of 219.

**Comment 4:** I cannot understand why SLE as a diagnosis was excluded with this heavy proteinuria that cannot be accounted for by either TB or HLH. It is more palatable to consider that the patient had lupus induced HLH and was complicated by reactivation of TB by immunosuppression received in the form of steroids.

**Response:** Thank you for your concerns about our manuscript. In previous studies, severe proteinuria correlated closely with HLH, and 24% of patients with HLH with AKI had nephrotic-range proteinuria (5-7). According to the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus, if a patient’ s symptoms can be explained by another disease, SLE should not be considered (4). In addition, our patient received methylprednisolone and hydroxychloroquine sulfate at admission, which are conventional category 1 drugs for SLE, but the patient's routine blood tests showed further reductions in blood count, which is rarely observed in SLE. Many studies have shown an association between nonadherence and a higher risk of flares, morbidity, hospitalization, renal failure and death (8-10). However, our patient received only antitubercular therapy without any treatment for SLE and attended telephone follow-up visits for more than a year. No signs of recurrence have been noted thus far. Therefore, we suspect that the diagnosis of SLE was incorrect.

**Reviewer 2**

**Comment 1:** For the case presentation, the Visiting time on the hospital should be noticed. Moreover, the exact time for the examinations should also be recommended.

**Response:** Thank you for your valuable advice. The patient' s first visit was 9 October 2019, after a 1-month history of sore throat, irregular fever and malaise, with temperatures up to 39.7°C. After admission, we performed physical examinations immediately. At the same time, laboratory examinations, such as routine blood tests, routine urine tests, liver function, hypofibrinogenemia and antibodies and imaging examinations, were carried out. Five days later, SLE was suspected, and category 1 drugs for SLE were started. Eight days later, the patient was discharged. Fifteen days after discharge, the patient was readmitted with fever. Laboratory examinations were performed again, and we conducted positron emission tomography (PET) and bone marrow aspiration. After 5 days, a sputum smear revealed acid-fast stain positivity.

**Comment 2:** It would be great if the treatment line figure should be added.

**Response:** Thank you for your thorough review and constructive comment. Below is the treatment timeline.

**Comment 3:** It is a pity that the patient was not followed up to outpatient. Therefore the routine blood tests after treatment were missing.

**Response:** Thank you for your concerns about our manuscript. Unfortunately, the patient was not followed up as an outpatient, with only telephone follow-up.

We would like to express our sincere appreciation to you for constructive and insightful comments on our paper. We look forward to hearing from you.

Best wishes,

Yi Yang

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