Answering Reviewers

Dear Editor and Reviewers:

We greatly appreciate the thorough and thoughtful comments provided on our submitted article. We have carefully addressed each of the comments given by the reviewers and made the appropriate revisions as indicated below.

Please let us know if you still have any questions or concerns about the manuscript. We will be happy to address them in a timely manner.

Sincerely,

Xiuli Sun

Comments from Reviewer #1:

1. In the INTRODUCTION: Because some audiences are not in the field of hematology. Please provide a brief introduction of predisposing factor or host factors for the developing of GC-SS, and the relationship between GC-SS and MDS.

We are thankful to the reviewer for pointing this out. We have revised the text to address your concerns and hope that it is now clearer.

We have **added** the text "According to available case reports, GC-SS tends to occur in patients with obesity, autoimmune diseases, and malignancies, including hematologic malignancies, such as myelodysplastic syndrome (MDS), multiple myeloma, and acute myeloid leukemia. The relationship between GC-SS and MDS remains to be elucidated." to the first paragraph of the INTRODUCTION.

2. In the CASE PRESENTATION: The diagnostic flow chart for the MDS is unclear. As an audience not in the field of hematology, why to arrange bone marrow aspiration and biopsy for the patients? How to make the

diagnosis of MDS? depending on the bone marrow finding? Please clearly define it.

We are grateful to the reviewer for pointing this out. To clearly illustrate the diagnostic process, we have ***rewritten*** the ***Laboratory examinations*** section and the **FIRST DIAGNOSIS** section, **as shown below:**

Laboratory examinations

Routine blood tests yielded the following results: low white blood cell count (1.82×10^9/L; normal range: 3.5-9.5 × 10^9/L); slightly low absolute neutrophil count (1.07×10^9/L; normal range: 1.8-6.3 × 10^9/L); low lymphocyte count (0.6 × 10^9/L; normal range: 1.1-3.2 × 10^9/L) with normal lymphocyte proportion (23.5%; normal range: 20%-50%); very low platelet (PLT) count (19 × 10^9/L; normal range: 125-350 × 10^9/L); and low hemoglobin level (53 g/L; normal range: 130-175 g/L). The red blood mean cell volume and mean corpuscular hemoglobin were within the normal ranges, as was the reticulocyte count (29.8 × 10^9/L; normal range: 25-112 × 10^9/L). Peripheral blood (PB) smear showed erythroblasts, oval erythrocytes, and teardrop-shaped red blood cells that were readily visible, with 3% myeloblasts. In addition, lactate dehydrogenase and C-reactive protein were elevated (351 IU/L; normal range: 109-245 IU/L and 84.4 mg/L; normal range: 0-8 mg/L, respectively). Folic acid and vitamin B12 levels were normal. Direct antiglobulin (Coombs) testing and paroxysmal nocturnal hemoglobinuria clone testing yielded negative results.

There was high suspicion of hematologic malignancy because of pancytopenia, splenomegaly, and increased blast cell count in PB. Bone marrow aspiration and bone marrow biopsy were performed to clarify the diagnosis. The bone marrow aspiration yielded a "dry" tap, even at the sternal level. Bone marrow biopsy showed the marrow to be hypercellular, with erythroid hyperplasia and a slight increase in granulocytic precursors; moreover, megakaryocytes were normal in number, and micromegakaryocytes and nonlobulated megakaryocytes were readily visible. The reticulin fibrosis

was grade 2 (designated MF-2), according to the World Health Organization grading for myelofibrosis. Flow cytometry and chromosomal and gene mutation testing were not performed due to the difficulties in obtaining bone marrow fluid.

FIRST DIAGNOSIS

The patient had pancytopenia, hypercellular bone marrow, marked dysplasia of the megakaryocytic lineage, 2%-4% myeloblasts in PB, no Auer rods, and grade-2 myelofibrosis; in accordance with the World Health Organization classification of MNs and acute leukemia[8], the patient was diagnosed with MDS with excess blasts-1 (commonly known as EB-1) associated with myelofibrosis. He was also diagnosed with an angioneurotic edema of the tongue and floor of the mouth.

3.1 In the DISCUSSION: In the 3rd and 4th paragraph, it is very confusing regarding to the diagnosis of SS, GS-SS, H-SS, and HGS-SS. Please provide a more clear definition of SS, GC-SS, H-SS, and HGS-SS.

We are very appreciative that the reviewer pointed this out. To make a clearer definition of SS, GC-SS, H-SS, and HGC-SS, we have added a new paragraph to detail the SS, as shown below:

SS is an uncommon inflammatory disorder characterized by an abrupt onset of painful erythematous plaques or nodules, histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, usually accompanied by fever and elevated inflammatory markers, such as neutrophils' count, erythrocyte sedimentation rate, and C-reactive protein[15]. Moreover, SS is often associated with a range of underlying disorders, such as hematologic or visceral malignancy, inflammatory disease, or pregnancy, or preceded by an upper respiratory or gastrointestinal infection or vaccination[16, 17].

We have also added the sentence: "SS with both the pathological characteristics of H-SS and the lesion features of GC-SS is HGC-SS." to the 5th paragraph.

3.2 In the 5th paragraph, the reviewer discussed SS and leukemia cutis (LC). It seems that LC is easily confused with the SS. However, in the CASE PRESENTATION, the author didn't mention it at all in the diagnostic flow chart. Suggest to add the differential diagnosis in the CASE PRESENTATION.

We are thankful to the reviewer for pointing this out. It is truly difficult to distinguish between H-SS and leukemia cutis (LC) by clinical and pathological features. We can differentiate the diagnosis by the effectiveness of treatment, as non-anti-leukemic regimens are not effective against LC.

As above, in order to ensure the coherence of the reader's thinking when reading the article, we have ***added*** the text "Because the combination of glucocorticoid and immunomodulatory therapy was effective in treating the lesion, and non-anti-leukemic regimens are not effective against LC, the diagnosis H-SS was confirmed while the possibility of LC was ruled out. This distinction is important because it is difficult to distinguish between H-SS and leukemia cutis by clinical and pathological features alone." to the **OUTCOME AND FOLLOW-UP** section.

4. In the CONCLUSION: It is only a case report focusing on the unusual presentation of SS. Therefore, it is hard to conclude that "Allo- HSCT may be able to overcome the detrimental effects of myelofibrosis on the prognosis of MDS". Please remove it.

We appreciate the reviewer for pointing this out. We have removed the sentence.

5. In the figure legend: The figure 1 included 12 pictures. However, the author didn't cite the corresponding figure (such as figure 1-A, 1-B…..) in the adequate text. Please revise it.

We are grateful to the reviewer for pointing this out. **We have made the revision according to the comment.**

Besides, figure 1-A,B,C are clinical picture for the patients. However, the author didn't mention the timing after sternal aspiration for each picture. Please also revise it.

We have added the time information in the figure legend of figure 1 A-C, as shown below:

Figure 1 Cutaneous manifestation and pathological characteristics. A: The skin lesion on the 7th d after sternal aspiration; B: The skin lesion on the 12th d after sternal aspiration; C: The skin lesion on the 7th d after prednisone therapy.

Comments from Reviewer #2:

>>In Figure 1A to C, authors should show the timing.

We are grateful to the reviewer for pointing this out. We have added the time information in the figure legend of figure 1 A-C, as shown below:

Figure 1 Cutaneous manifestation and pathological characteristics. A: The skin lesion on the 7th d after sternal aspiration; B: The skin lesion on the 12th d after sternal aspiration; C: The skin lesion on the 7th d after prednisone therapy.

>>In present case, authors described that focal infection was ruled out by next-generation sequence. Authors should show the detail.

We appreciate the reviewer for pointing this out. We have added the text" *Next-generation sequencing of the biopsy specimen, based on the Illumina platform (iSeq 100 Sequencing System), covering 9694 bacteria, 1551 fungi, 6761 viruses, 144 mycobacteria, 305 parasites, and 107 mycoplasma/chlamydia, was negative.*" to the end of the last paragraph of **CHANGES IN CONDITION.**

>>A figure showing the clinical course such as fever, CRP and treatment might be helpful for readers to understand.

We are thankful to the reviewer for pointing this out. We have added a figure to show the body temperature changes and medication administration to help readers to understand the clinical course, as shown below:

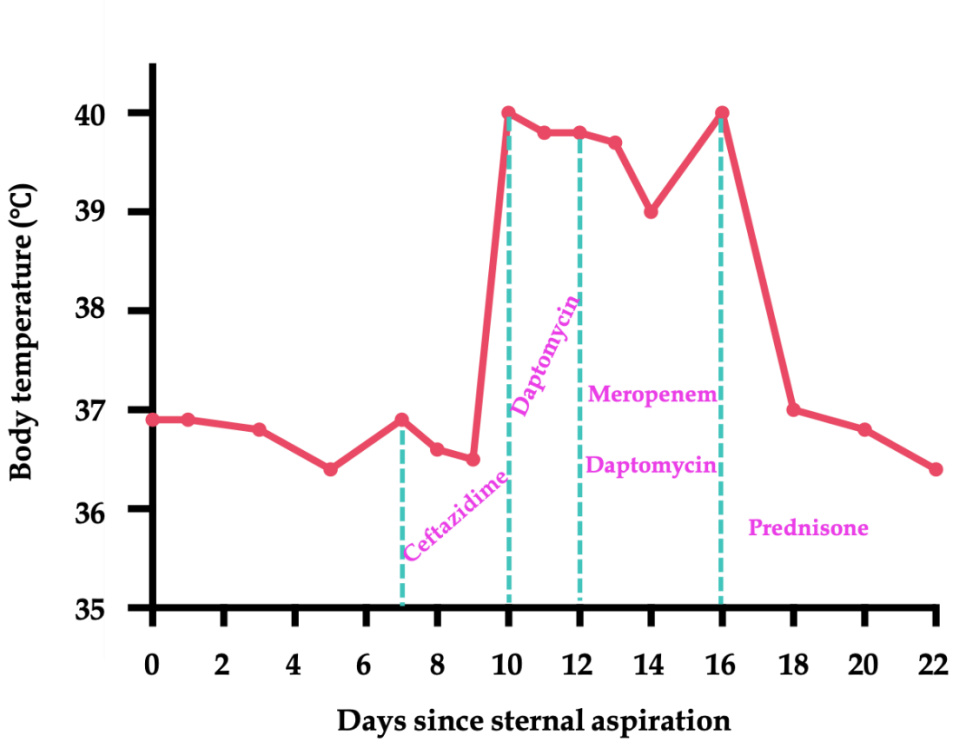

Figure 2 Body temperature chart and medication administration. The x-axis represents the number of days since the sternal aspiration and the y-axis

represents the body temperature. Between the light green dashed lines, the drugs used on the corresponding dates are listed.

Comments from Re-reviewer:

The author reported a patient diagnosed as MDS combined with the unusual presentation of HGC-SS. The author discussed with unusual variant of SS and the possible prognostic factor of SS and MLC for patients with MN. The author has appropriately addressed the questions raised during the peer-review. Suggest to receive the revised manuscript.

Thanks for your comments.