Dear Editor of World Journal of Clinical Cases

We would like to thank editors of World Journal of Clinical Cases and unknown reviewers of our manuscript for carefully reading our manuscript and providing such valuable comments. We have addressed the concerns of the respected editor and reviewers as follows.

It is worth mentioning that in the revised manuscript, the updated text appears in blue colour.

Kind Regards

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Answering to Reviewer #1:

Reviewer's Comment:

1 Did the Severe aplastic anemia, and PNH cause the leukemic transformation? Or was the leukemia an unexpected event, regardless of the pathogenesis of PNH/SAA? What was the effect of tuberculosis and of the treatment for tuberculosis? Please provide a novel paragraph in the discussion explaining these questions in a simple way and try to be as specific as possible.

We have addressed the above questions in 2 paragraphs.

One revised paragraph as "First, active tuberculosis can repress normal hematopoiesis in predisposed patients, inducing AHF. A few cases of aplastic cytopenia have been reported to be associated with disseminated

tuberculosis[14-17] and even with Bacillus Calmette-Guerin (BCG) vaccination[18]. Th1 immune responses are the major defense mechanism against tuberculosis[19-21], and *Mycobacterium tuberculosis* antigens can directly activate Th1 responses[21,22]. Activated Th1 responses lead to production of a large amount of type I inflammatory cytokines[19-22] and thereby suppress host autologous hematopoiesis[23,24], which is the immunological signature of AA and hypoplastic MDS (hMDS)[1,25,26]. Currently, tuberculosis is still the commonest infectious disease[27,28], and its contribution to autoimmune diseases has been extensively investigated[29]. Despite great advances in recent decades, it is estimated that nearly a quarter of the world's population is latently infected with *M. tuberculosis*[30,31]. When host immune function is compromised under certain conditions, such as aging, malnutrition, administration of immune suppressants due to treatment for autoimmune disorders, aggravation of psychological distresses, comorbidity of chronic organ dysfunction or coinfection with other pathogenic factors, latent tuberculosis can become reactivated. Active tuberculosis recalls specific and nonspecific responses due to the increased antigen load. Trained Th1 cells[32,33], cytotoxic T lymphocytes (CTLs)[34], natural killer (NK)/NKT cells[35,36], unconventional lymphocytes[37,38] and even CD5+ (B1) B cells[39] respond to antigen stimulation, secrete a large amount of IFN-γ, TNF-α and other proinflammatory factors and suppress granulopoiesis, erythropoiesis and megakaryocytopoiesis[23,24]. Immune dysregulation can occur not only in active disease but also in latent infection due to the high heterogeneity of bacterial toxicity and host immune competence[40,41]." (Reflected in page 13 line 14 to page 14 line112)

One added paragraph as "Although disease phenotypic transformations occurred unexpectedly in this patient, it is not surprising that disseminated tuberculosis can repress leukemic hematopoiesis. Th1 immune responses are the major mechanism in defense against tuberculosis[19-22], and excessive Th1

immune responses can effectively repress granulopoiesis, erythropoiesis and megakaryocytopoiesis[23-25], including leukemic clones[61-63]. During active tuberculosis, our patient manifested aplastic pancytopenia, and when antigen stimulation was removed due to effective treatment of her tuberculosis, leukemic clones penetrated, suggesting that leukemic clones preexisted but were suppressed in the PNH and SAA stages. This is because development of a symptomatic myeloid neoplasm through acquisition and accumulation of novel oncogenic mutations is unlikely in an interval of only 7 months. From this point of view, a chronic inflammatory milieu indeed serves as an antileukemic mechanism[17,61]. Leukemic evolution is the result of immune escape due to the elevated antileukemic threshold and immune exhaustion in the advanced stage[77,78]" (Reflected in page 16 line 28 to page 17 line 14).

2 In the Introduction section, many elements of the case presentation are described. Please remove them and place them to the case presentation part of the manuscript.

We have succinctly rewritten this part as"This case study reports a middle-aged Chinese woman with a 6-year history of non-SAA and a 2-year history of paroxysmal nocturnal hemoglobinuria (PNH). With reactivation of tuberculosis infection, SAA developed, and hemoglobinuria disappeared. However, the disease phenotype was transformed into AML with mutated *NPM1* after a short duration of hematological remission during anti-tuberculosis treatment." (Reflected in page 6 line 12-18).

3 Are there other SAA-PNH cases in the literature, which transformed to AML? Please answer that to the discussion.

We have added sentences to reply the comments as "Although spontaneous transformation from SAA and PNH to advanced myeloid neoplasms has been reported[84,85] and is usually ascribed to a selective advantage over normal compartments under intensive immunological pressure due to acquisition and accumulation of novel oncogenic mutations and escape of immune

surveillance due to immune exhaustion in chronic inflammatory milieu[77,78], the transformation process is very long, which is distinct from the process described for this patient." (Reflected in page 18 line 13-20).

4 Are there other only PNH cases in the literature, which transformed to AML? Please answer that to the dicsussion.

We have added sentences to reply the comments as "Although spontaneous transformation from SAA and PNH to advanced myeloid neoplasms has been reported[84,85] and is usually ascribed to a selective advantage over normal compartments under intensive immunological pressure due to acquisition and accumulation of novel oncogenic mutations and escape of immune surveillance due to immune exhaustion in chronic inflammatory milieu[77,78], the transformation process is very long, which is distinct from the process described for this patient." (Reflected in page 18 line 13-20).

5 Did the patient receive chemotherapy before the allo-HSCT and what was that?

We have added the chemotherapy before allo-HSCT (Reflected in page 12 line 25-29).

6 Do the AHF syndromes protect or cause the leukemic transformation? Please answer that to the discussion in a separate paragraph and provide published evidence.

AHF itself may be an antileukemic mechanism against malignant proliferation. Th1 immune responses in response to intracellular pathogen infections suppress normal and leukemic hematopoiesis with preferential suppression of myeloid malignant cells. Deranged Th1 immune responses are the characteristic immunological signature in AHF, which is the same as the immune responses in response to intracellular pathogen infections. We have cited the related studies (Reflected in page 13 line 14 to 11 line 14, page 16 line 28 to page 17 line 14).

7 What are the mechanisms published possibly explaining that an infection might cause spontaneous remission to an AML and how long does this remission last?

The contribution of infection to spontaneous remission in AML is usually ascribed to the restoration of immune surveillance against leukemic cells. Immune exhaustion characteristic of high expression of negative regulatory molecules on immune cells and high concentration of negative regulatory cytokines in host plasma is the immunological signature in AML patients. When patients achieve hematological remission, the negative immune response-predominated signature transformed to a positive immune response-predominated signature. However the remission duration is frequently very short, and relapses occur frequently within 2-3 months. We have revised the sentences as "Inflammatory stress-fueled antileukemic activities can also be inferred from spontaneous remission in AML[64-66]. To date, spontaneous remission has been reported in more than 200 AML patients. It occurs frequently following an infectious episode and aplastic cytopenia. The occurrence of spontaneous remission is usually ascribed to reversion of the immune exhaustion state and restoration of antileukemic activities due to secretion of a substantial amount of proinflammatory cytokines against invading pathogens[65-67]. In most cases, the remission duration is very short, and symptomatic AML frequently reemerges within 2-3 months, indicating that the leukemic clones are not eradicated, even in inflammatory stress-fueled antileukemic activities[68]." (Reflected in page 16 line 3-13).

8 Could antithymocyte globulin or cyclosporine have caused the leukemic transformation or they acted against that? Please answer that to the dicsussion. In general, write in a simple way and explain better, being more specific, instead of analyzing theories in the discussion.

ATG plus cyclosporine-based ISTs relive the inflammatory stress-fueled antileukemic activities through depletion of autoimmune CTLs, therefore promoting leukemic transformation. We have revised the sentences as "Leukemic transformation in SAA patients following IST also suggests that autoimmunity in AHF operates as an antileukemic mechanism. hMDS is another acquired form of AHF. In hMDS patients, clonal expansion is a common dilemma with IST[81,82], providing alternative evidence for the contribution of autoimmune responses to suppressive activities against leukemic clones. Autoimmune responses in AHF target leukemic clones[60,61], whereas IST deletes autoimmune CTLs[83], promoting expansion of leukemic clones and penetration of symptomatic neoplasms. The effect of IST may be similar to that of treatment for underlying infections on leukemic transformation: while treatment of underlying infections removes immune-activating factors, IST intervenes in the immune attack pathology."(Reflected in page 17 line 29 to page 18 line 11).

9 Please explain that according to the ICC classification, since the NPM1 mutation was found, the case is an AML regardless of the percentage of blasts if they exceed 10% (16% in the described case). That is why IT IS NOT AN MDS. Please explain that to the discussion.

We have revised the diagnosis as "AML with mutated *NPM1*".

10 Please correct PHN is wrong and PNH is correct (in some parts of the manuscript). Moreover please correct the phrase in line 30 of the case summary .....SAA had BEEN transformed into.....is the correct phrase.

We have revised "PHN" into the correct form of "PNH" throughout the manuscript. We have revised the phrase "had transformed" to "had been transformed" in the section of ***CASE SUMMARY.***