86528_Auto_Edited.docx

WORD COUNT	3765	TIME SUBMITTED	19-AUG-2023 07:44PM
		PAPER ID	102101475

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 86528

Manuscript Type: CASE REPORT

Leukemic transformation during anti-tuberculosis treatment in aplastic anemia-paroxysmal nocturnal hemoglobinuria syndrome: A case report and review of literature

Nuan-Nuan Xiu, Xiao-Dong Yang, Jia Xu, Bo Ju, Xiao-Yun Sun, Xi-Chen Zhao

Abstract

BACKGROUND

Accumulating evidence demonstrates that autoimmune hematopoietic failure (AHF) and myeloid neoplasms have an intrinsic relationship with regard to clonal hematopoiesis and disease evolution. In approximately 10%–15% of patients with severe aplastic anemia (SAA), the disease phenotype is transformed into myeloid neoplasms following antithymocyte globulin plus cyclosporine-based immunosuppressive therapy (IST). In some of these patients, myeloid neoplasms appear during or shortly after IST. Leukemic transformation in SAA patients during anti-tuberculosis treatment has not been reported.

CASE SUMMARY

A middle-aged Chinese woman had a 6-year history of non-SAA and a 2-year history of paroxysmal nocturnal hemoglobinuria (PNH). With aggravation of systemic inflammatory symptoms, severe pancytopenia developed, and her hemoglobinuria disappeared. Laboratory findings in cytological, immunological and cytogenetic analyses of bone marrow samples met the diagnostic criteria for "SAA". Definitive diagnosis of disseminated tuberculosis was made in the search for infectious niches. Remarkable improvement in hematological parameters was achieved within one month of anti-tuberculosis treatment, and complete hematological remission was achieved within four months of treatment. Frustratingly, the hematological response lasted for only 3 mo, and pancytopenia reemerged. At this time, cytological findings (increased bone marrow cellularity and an increased percentage of myeloblasts that accounted for 16% of all nucleated hematopoietic cells), immunological findings [increased percentage of cluster of differentiation (CD)34+ cells that accounted for 12.28% of all nucleated hematopoietic cells] and molecular biological findings [identification of somatic mutations in *nucleophosmin-1* (*NPM1)* and casitas B-lineage lymphoma (CBL) genes] revealed that "SAA" had been transformed into acute myeloid leukemia (AML) with mutated *NPM1*. The transformation process suggested that the leukemic clones had

preexisted but were suppressed in the PNH and SAA stages, as development of symptomatic myeloid neoplasm through acquisition and accumulation of novel oncogenic mutations is unlikely in an interval of only 7 mo. Aggravation of inflammatory stressors due to disseminated tuberculosis likely contributed to the repression of normal and leukemic hematopoiesis, and the relief of inflammatory stressors due to anti-tuberculosis treatment contributed to penetration of neoplastic hematopoiesis. The concealed leukemic clones in the SAA and PNH stages raise the possibility of an inflammatory stress-fueled antileukemic mechanism.

CONCLUSION

Aggravated inflammatory stressors can repress normal and leukemic hematopoiesis, and relieved inflammatory stressors can facilitate penetration of neoplastic hematopoiesis.

Key Words: Case report; Aplastic anemia; Paroxysmal nocturnal hemoglobinuria; Acute myeloid leukemia; Tuberculosis; Leukemic transformation

Xiu NN, Yang XD, Xu J, Ju B, Sun XY, Zhao XC. Leukemic transformation during anti-tuberculosis treatment in aplastic anemia-paroxysmal nocturnal hemoglobinuria syndrome: A case report and review of literature. *World J Clin Cases* 2023; In press

Core Tip: A Chinese woman had a 6-year history of nonsevere aplastic anemia and a 2-year history of paroxysmal nocturnal hemoglobinuria. With aggravation of systemic inflammatory symptoms, severe pancytopenia developed, and her hemoglobinuria disappeared. Laboratory findings met the diagnostic criteria for "severe aplastic anemia". Anti-tuberculosis treatment resulted in leukemic transformation after a short duration of hematological remission. This case study reveals that aggravated inflammatory stressors can repress normal and leukemic hematopoiesis and relieved

inflammatory stressors can facilitate penetration of neoplastic hematopoiesis, suggesting an inflammatory stress-fueled antileukemic mechanism.

INTRODUCTION

Acquired aplastic anemia (AA) is the paradigm of autoimmune hematopoietic failure (AHF). AA is generally considered a benign hematological disease resulting from autoimmune destructive impairment of hematopoietic progenitor cells (HPCs)[1,2]. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are well-known myeloid neoplasms resulting from somatic mutations that drive leukemic hematopoiesis[3-5]. In approximately 10%–15% of patients with severe aplastic anemia (SAA), the disease phenotype is transformed into MDS or AML following antithymocyte globulin (ATG) plus cyclosporine-based immunosuppressive therapy (IST)[6-8]. However, leukemic transformation in SAA patients during anti-tuberculosis treatment has not been reported. 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.

CASE PRESENTATION

Chief complaints

The chief complaint was aggravating fatigue for 3 mo.

History of present illness

Eight years prior, the 39-year-old Chinese woman experienced aggravating fatigue and was found to have pancytopenia. Diagnosis of non-SAA was made based on heavily reduced bone marrow (BM) cellularity and hematopoietic volume on aspirates and biopsy, decreased percentage of cluster of differentiation (CD)34+ hematopoietic

progenitors on immunological analysis of BM samples, and normal 46,XX karyotype on cytogenetic analysis of cultured BM cells. The patient was treated with cyclosporine (75 mg, three times daily) and stanozolol (2 mg, three times daily). With this immune suppressant treatment, complete hematological remission was achieved within 7 mo. Cyclosporine and stanozolol treatment was continued. Complete remission was maintained until hemoglobinuria occurred 2 years prior. Diagnosis of PNH was made based on an increase in BM cellularity and the percentage of erythroid progenitors (52.5% of all nucleated cells), a decrease in the percentages of CD55 and CD59 expression (7.85% and 11.98% on erythrocytes and 3.56% and 7.26% on granulocytes, respectively), normal 46,XX karyotype and negative Coombs test. Sodium bicarbonate (1.0 g, three times daily) was added. During the treatment of PNH, her complete blood cell (CBC) count results generally fluctuated within the following ranges: white blood cells (WBCs), 4.00–6.00×10^9/L; red blood cells (RBCs), 2.40–2.80×10^{12}/L; hemoglobin levels (Hb), 100–110 g/L; platelets (Plts), 130–180×10^9/L; and absolute reticulocyte counts (Ret), 110–150×10^9/L.

Beginning 3 mo prior to this admission, the patient experienced aggravating fatigue that was far more severe than the degree of anemia. Subjective fever, weight loss, night sweats, loss of appetite, and abdominal distension were complained. Several febrile episodes occurred during this period. Intravenous antibiotic treatments at another hospital relieved the febrile episodes, but elevated inflammatory indices [C-reactive protein (CRP) and fibrinogen] persisted. With repeated febrile episodes, pancytopenia developed, and hemoglobinuria disappeared. The patient was sent to our hospital during this febrile episode.

History of past illness

The patient denied having diseases affecting the cardiovascular, endocrine, respiratory, gastrointestinal, hematological, urogenital or musculoskeletal systems before diagnosis of non-SAA was made.

Personal and family history

No family history of inherited, hematological, rheumatological or malignant diseases was recorded.

Physical examination

The patient was 157 cm tall and weighed 47.0 kg. Her vital signs were as follows: body temperature, 38.2 ˚C; respiratory rate, 20 breaths per minute; heart rate, 96 beats per minute; and blood pressure, 122/79 mmHg. Physical examination revealed the presence of mild tenderness of the right lower quadrant. There were no significant abnormalities in the nervous, respiratory, cardiovascular, or musculoskeletal systems.

Laboratory examinations

Routine laboratory examinations

On admission, the CBC showed the following results: WBCs, 2.10×10^9/L; absolute neutrophil count (ANC), 0.46×10^9/L; RBCs, 1.02×10^{12}/L; Hb, 49 g/L; Plts, 25×10^9/L; Ret, 7.50×10^9/L; and CRP, 142.5 mg/L. Her coagulation profile showed an elevated serum fibrinogen concentration (4.070 g/L), with a D-dimer level of 0.02 mg/L. Biochemical tests showed a mildly decreased level of albumin (34.6 g/L) in the absence of abnormalities in markers of liver and renal function. Multiple pathogenic cultures of blood samples reported no growth of Gram-positive and Gram-negative bacteria. Negative serological test results for hepatitis virus A, B, and C and human immunodeficiency virus (HIV) were obtained. Biological tests for Epstein–Barr virus (EBV) and parvovirus B19 (PB19) DNA were negative. Lymphocyte subgroup analysis revealed an increased percentage of the CD8+ population and decreased percentages of the CD4+ and CD19+ populations. Serum levels of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were elevated, indicating activation of T helper type 1 (Th1) immune responses. The IFN-γ release assay was positive. Aspirate from ascites was bloody and exudative. with an increased number and percentage of mononuclear cells and an elevated level of adenosine deaminase.

Specific laboratory examinations for blood diseases

Cytological evaluation of BM smears (Figure 1A) showed heavily decreased cellularity with a paucity of myeloblasts. Immunological analysis of BM samples revealed a significant decrease in percentages of CD34+ cells (0.27%), CD19+ cells (4.62%), and CD4+ cells (8.18%) and an increase in those of CD8+ cells (24.04%), CD5+ cells (8.22%) and CD57+ cells (15.77%), consistent with the immunological profile of Th1 immune responses in the BM environment. Normal blood expression levels of CD55 and CD59 (97.83% and 96.18% on erythrocytes and 99.25% and 98.63% on granulocytes, respectively) confirmed the absence of PNH clones. Cytogenetic analysis showed a normal 46,XX karyotype. Both direct and indirect Coombs tests were negative. These laboratory data met the Camitta diagnostic criteria for "SAA"[9] and indicated that the disease phenotype had been transformed from PNH to SAA.

Imaging examinations

Because the patient presented with systemic inflammatory symptoms, computed tomography (CT) scans were performed to search for inflammatory niches. Radiological findings on chest (Figure 2) and abdominopelvic (Figure 3) CT suggested reactivation of tuberculosis. Tuberculosis infected the lungs, pleura, mediastinum, intestines, celiac lymph nodes and peritoneum[10,11]. Definitive diagnosis of active tuberculosis was made due to identification of acid-fast bacilli in sputum.

FINAL DIAGNOSIS

The patient was diagnosed with SAA complicated by disseminated tuberculosis reactivation.

TREATMENT

After disseminated tuberculosis was diagnosed, the patient was prescribed the standard anti-tuberculosis treatment modality: a combination of rifampicin (0.45 g/d), isoniazid (0.3 g/d), ethambutol (1.0 g/d), and pyrazinamide (1.0 g/d) for 2 mo and subsequently

a combination of rifampicin and isoniazid for 6 mo. Other treatments included recombinant human granulocyte colony-stimulating factor (rhG-CSF) for severe neutropenia and supportive care for anemia.

OUTCOME AND FOLLOW-UP

Her systemic inflammatory symptoms quickly became ameliorated, the pulmonary exudative lesions and ascites were gradually absorbed, and her performance status was significantly improved. One month later, the WBCs, ANC, Plts and Ret on CBC monitoring increased remarkably. Four months of anti-tuberculosis treatment led to normalization of hematological parameters. CBC results at the peak time showed WBCs at 7.45×10^9/L, ANC at 4.49×10^9/L, RBCs at 3.66×10^{12}/L, Hb at 127 g/L, Plts at 274×10^9/L, and Ret at 66.71×10^9/L.

Frustratingly, this hematological response lasted for only 3 mo, and pancytopenia reemerged during anti-tuberculosis treatment. At this time, morphological reevaluation of BM smears showed that the cellularity had become hyperplastic, with a remarkable increase in the percentage of myeloblasts, accounting for 16% of all nucleated cells (Figure 1B). Immunological analysis of the BM samples revealed an increased percentage of CD34+ cells, which accounted for 12.28% of nucleated cells. Molecular biological analysis identified myeloid neoplasm-associated gene mutations in *nucleophosmin-1* [*NPM1*, with a variant allele frequency (VAF) of 32.55%] and casitas B-lineage lymphoma (CBL, with a VAF of 38.26%). The laboratory data met the diagnostic criteria for AML with mutated *NPM1*[12,13]. One course of DA3+7 (daunorubicin, 60 mg/d, d1-3; cytarabine, 200 mg/d, d1-7) chemotherapy led to complete remission. After another course of DA3+7 chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) was performed. At the time this manuscript was finished, 11 mo had passed since allo-HSCT had been performed, and the patient remained in complete remission.

DISCUSSION

In this patient, aplastic cytopenia developed during an inflammatory episode due to disseminated tuberculosis reactivation. During active tuberculosis, BM cellularity became hypoplastic, with disappearance of PNH clones and absence of evident leukemic clones. The increased percentage of the CD8+ lymphocyte population and elevated serum levels of IFN-γ and TNF-α indicated activation of Th1 response-mediated autoimmunity. With effective anti-tuberculosis treatment, the disease phenotype was transformed from AHF into an advanced myeloid neoplasm. This case study highlights the following intriguing points that are of great significance in theoretical research and clinical practice.

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].

Tuberculosis-associated aplastic cytopenia has been reported in disseminated tuberculosis instead of isolated pulmonary tuberculosis, which suggests that effective suppression of host hematopoiesis critically requires an additional inflammatory condition with an intensity that is maintained by sufficient activated immune cells and a large amount of proinflammatory mediators. In this patient, tuberculosis infected the lungs, pleura, mediastinum, intestines, celiac lymph nodes and peritoneum. Gut involvement of tuberculosis infection has a more potent influence on the systemic inflammatory state and thus likely plays a more important role in AHF development[42] because the gastrointestinal tract can provide sufficient activated immune cells and continuously supply intestine-derived antigens[43,44] from not only pathogenic bacteria but also commensal microbes[45,46]. In our investigation of inflammatory niches in SAA patients during inflammatory episodes, 5 of 17 recruited patients had imaging abnormalities suggestive of tuberculosis reactivation, all involving the gastrointestinal tract[47]. Gastrointestinal infections can induce inflammatory lesions not only in infected segments but also in noninfected segments through induction of gut dysbiosis[48-50]. In gut dysbiosis and gut inflammatory disorders, impaired intestinal barrier functions allow close contact between intestine-derived antigens and host immune cells, thereby activating immune cells and creating an inflammatory milieu at an intensity sufficient to initiate and sustain autoimmunity in remote organ systems[50,51]. A gluten-free diet in celiac disease-associated aplastic cytopenia[52], resection of diseased colonic segments in neutropenic enterocolitis[53] and effective treatment of gut inflammatory disorders in aplastic crisis[54] can effectively relieve autoimmune responses and facilitate restoration of autologous hematopoiesis, reinforcing the role of inflammatory conditions in AHF pathogenesis[44]. In an animal model of AHF using allogenic hematopoietic stem cell transplantation (allo-HSCT), it

has been known for a long time that induction of aplastic cytopenia critically required engagement of gut inflammatory milieu[55].

Second, aggravated inflammatory stressors due to active tuberculosis can suppress PNH clones, resulting in so-called "spontaneous remission". Spontaneous remission in PNH has been reported, frequently following an infectious episode[56,57]. Disappearance of PNH clones during inflammatory episodes suggests that loss of glycosylphosphatidylinositol-anchored proteins likely enhances the tolerance of inflammatory cytokine-induced apoptosis rather than complete loss of the hematopoietic regulatory mechanisms in PNH clones[58,59]. In an intensive inflammatory milieu, PNH clones can be heavily suppressed. Spontaneous remission in PNH may be caused by an intensive inflammatory milieu due to fulminant inflammatory episodes through hematopoietic regulatory mechanisms.

Third, the most intriguing phenomenon is that active tuberculosis can repress leukemic hematopoiesis, leading to concealment of leukemic clones in SAA and PNH stages. This phenomenon raises the possibility that autoimmune responses in AHF may involve an antileukemic mechanism[60,61]. In this case, leukemic clones were concealed during active tuberculosis and penetrated during anti-tuberculosis treatment, suggesting that inflammatory stressors strengthened antileukemic activities and preferentially repressed leukemic clones[62,63]. 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 mo, indicating that the leukemic clones are not eradicated, even in inflammatory stress-fueled antileukemic activities[68]. Another phenomenon also suggests the existence of inflammatory stress-fueled antileukemic activities. A fraction of AML

patients experience a period of prolonged hematopoietic suppression after intensive chemotherapy during which repeated or durable infectious episodes are the major complication. If patients survive prolonged hematopoietic suppression, they may experience deep remission, a longer remission duration and a lower probability of relapse[69,70]. Recombinant IFN-α[71,72], immune checkpoint inhibitors[73,74] and BCG vaccination[75,76] have been successfully used in treatment of hematological malignancies, and the major adverse event is hematological toxicity. Much evidence supports the hypothesis that inflammatory stressors, induced either by infectious episodes or administration of immune-activating agents, can strengthen antileukemic activities. With relief of inflammatory stressors, the concealed leukemic clones expand, and the disease phenotype is transformed into symptomatic myeloid neoplasms.

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 mo. 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].

With widespread application of the next-generation sequencing (NGS) technique in diagnosis and risk stratification of hematological diseases[79], it has been found that approximately one-third of definitively diagnosed SAA patients harbor somatic mutations that are the well-known driver genetic abnormalities of myeloid neoplasms,

although the number and clone size of mutant genes are smaller than those in MDS[7,8,26,80]. In approximately 10-15% of SAA patients, the disease phenotype is transformed from SAA into myeloid neoplasms following ATG-based IST. In some of these patients, leukemic transformation appears during or shortly after IST[6-8]. Moreover, approximately 20%-30% of SAA patients fail to respond to IST, and these patients harbor a high frequency of unfavorable somatic mutations that are predictors of poor prognosis in myeloid neoplasms. Even in patients achieving a hematological response, the presence of unfavorable somatic mutations predicts a significantly increased risk of leukemic transformation[7,8]. 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 depletes 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. Accumulating evidence demonstrates that AHF and myeloid neoplasms have an intrinsic relationship regarding clonal hematopoiesis and disease evolution[77,78,80]. 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.

AA, PNH, hMDS and hAML are typical forms of AHF. Organ-specific autoimmunity is present mainly in the BM, suggesting that a primary immune-active environment

exists[86-88]. In addition to pathogenic microbes that can survive in the BM in which exogenous antigens induce immune responses[89-91], neoplasm-associated antigens[81,92] or damage-associated molecular patterns (DAMPs)[93,94], as the genetic or epigenetic products of genetically damaged HPCs, can initiate a primary immune-active BM environment and determine organ specificity. If the primary immune responses target neoplasm-associated antigens or DAMPs, they can represent an antileukemic mechanism. However, if the immune responses target antigens of less immunogenicity, the intensity of the primary immune-active BM environment may not be able to repress normal and leukemic hematopoiesis. In this situation, effective suppression of normal and leukemic hematopoiesis requires engagement of an additional inflammatory condition to strengthen antileukemic activities. In a chronic inflammatory environment, upregulated expression of Toll-like receptors (TLRs), the Nlrp3 inflammasome and human leucocyte antigen-DR (HLA-DR) increases sensitivity to antigen stimulation[94-96]. Even in the presence of inflammatory stress-fueled antileukemic activities, leukemic clones may not be eradicated[68], resulting in disease chronicity in the presence of additional inflammatory stressors and leukemic transformation after removal of inflammatory stressors through treatment of underlying inflammatory disorders[61,63] or IST[6-8], which can reasonably explain the high frequency of leukemic evolution following IST.

This finding suggests that patients with myeloid neoplasms who are ineligible for intensive treatments or receive maintenance therapy can be treated with immune-modifying agents, such as recombinant IFN-α, some types of endotoxins, immune checkpoint inhibitors, poly I:C, BCG vaccination or a combination modality, to artificially create an appropriate chronic or intermittent inflammatory milieu.

Limitations of this case study include the following: 1) the precise mechanism of the role of tuberculosis in the initiation of AHF and antileukemic activities was not elucidated; 2) the difference in suppressive activities between normal and leukemic hematopoiesis was not elucidated; and 3) more cases are needed to validate the exact role of tuberculosis in strengthening antileukemic activities.

CONCLUSION

Disseminated tuberculosis can cause AHF, suppressing both normal and leukemic hematopoiesis. Inflammatory stressors due to active tuberculosis may strengthen antileukemic activities of immune surveillance against malignant proliferation. Removal of inflammatory stressors due to anti-tuberculosis treatment may facilitate expansion of leukemic clones and penetration of symptomatic myeloid neoplasms. This finding suggests that patients with myeloid neoplasms who are ineligible for intensive treatments or receive maintenance therapy can be treated with immune-activating agents to artificially create an appropriate chronic or intermittent inflammatory condition, which may favor patient survival.

ACKNOWLEDGEMENTS

The authors thank Fan-Jun Meng (Department of Hematology, The Affiliated Hospital of Qingdao University) for his assistance in the analysis, diagnosis and treatment of the patient and in the revision of this manuscript.

86528_Auto_Edited.docx

ORIGINALITY REPORT

11%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.wjgnet.com Internet	193 words — 5%
2	f6publishing.blob.core.windows.net Internet	168 words — 4%
3	Xiao-Dong Yang, Bo Ju, Jia Xu, Nuan-Nuan Xiu, Xiao-Yun Sun, Xi-Chen Zhao. "Glucocorticoid-induced thrombotic microangiopathy in paroxysmal nocturnal hemoglobinuria: A case report and review of literature", World Journal of Clinical Cases, 2023 Crossref	30 words — 1%
4	mro.massey.ac.nz Internet	17 words — < 1%
5	jneuroinflammation.biomedcentral.com Internet	16 words — < 1%
6	www.ncbi.nlm.nih.gov Internet	14 words — < 1%
7	R F Price. "Acute head drop after cervical hyperflexion injury", Journal of Neurology Neurosurgery & Psychiatry, 5/1/2004 Crossref	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS