Glucocorticoid and Antibiotic Treatment-induced Recapitulated Hematological Remissions in Acute Myeloid Leukemia: Implications for Ligand-dependent Growth and Survival Advantage

Xiao-Yun Sun

The Central Hospital of Qingdao West Coast New Area

Shu-Xin Xiao

The Affiliated Hospital of Qingdao University

Xiao-Qiu Yang

The Central Hospital of Qingdao West Coast New Area

Xiao-Dong Yang

The Central Hospital of Qingdao West Coast New Area

Fan-Jun Meng

The Affiliated Hospital of Qingdao University

Xi-Chen Zhao (✉ zhaoxichen2003@163.com)

The Central Hospital of Qingdao West Coast New Area <https://orcid.org/0000-0002-3304-2851>

Case report

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Abstract

Leukemia-transformed multipotential hematopoietic cells have acquired the increased self-renewal capacity and impaired myeloid differentiation to mature blood cells. The emergence of symptomatic leukemia also critically requires the acquisition of growth and survival advantage in leukemic cells. Untreated leukemia patients usually demonstrated a progressive process. However, spontaneous remission occasionally occurred in a very small number of leukemia patients, which frequently followed a febrile episode and antibiotic treatment and was generally attributed to the activation of anti-neoplastic activities. Here we report a 63-year-old Chinese man who presented with the main complaints of abdominal pain, febrile episode and urticaria-like skin lesions. He was diagnosed with acute myeloid leukemia (AML-M4) with t(8;21)(q22;q22)/RUNX1-RUNX1T1 on the basis of morphological, immunological, cytogenetic and molecular analysis. He also had a mutated *FLT3-TKD* gene. He was treated with antibiotics and glucocorticoid for the gastrointestinal infection and the urticaria-like skin lesions. The infection and skin lesions were quickly resolved. Unexpectedly, along with the relief of the febrile episode, abdominal symptoms and skin lesions, he achieved a hematological remission. After relapse, repeating this treatment resulted in the second hematological remission. These recapitulated treatment responses strongly suggested that inflammatory stresses arising from the gut inflammatory lesions, which could be largely mitigated by antibiotic and glucocorticoid treatment, sustained the growth and survival advantage of the leukemic cells.

Background

Acute myeloid leukemia (AML) is a malignant hematological disease caused by a sequence of somatic mutations in multipotential hematopoietic cells. Leukemia-transformed multipotential hematopoietic cells have acquired the enhanced self-renewal capacity and the impaired myeloid differentiation to mature blood cells. The emergence of symptomatic AML not only requires the acquisition of increased self-renewal capacity but also critically requires the acquisition of growth and survival advantage in leukemic cells. It is the growth and survival advantage that lead to the accumulation and infiltration of a large amount of clonal leukemic cells in the bone marrow, taking up the hematopoietic pool, inhibiting the polyclonal normal hematopoiesis and ultimately resulting in the decreased capacity of producing mature blood cells. Anemia due to the decreased production of red blood cell, spontaneous hemorrhage due to the decreased production of platelet, and infection due to the decreased production of mature white blood cell are the major clinical presentations in AML patients [1–3].

Chemotherapy is currently the main initial treatment for AML, the aim of which is to reduce the large amount of leukemic cells and to achieve a complete hematological remission. Untreated AML patients usually demonstrated a progressive process [1]. However, spontaneous remission occasionally occurred in a very small proportion of untreated AML patients, which frequently followed a febrile episode and antibiotic treatment and was generally attributed to the activation of anti-neoplastic activities [5–12]. This spontaneous remission could occur not only in patients with recurrent cytogenetic abnormalities but also in patients with gene mutations in transcription factors. Here, we report a AML patient with t(8;21)

(q22;q22)/RUNX1-RUNX1T1 who achieved an unexpected hematological remission after antibiotic and glucocorticoid treatment for his abdominal infection and the urticaria-like skin lesions. After relapse, repeating this treatment resulted in the second hematological remission, suggesting the recapitulated treatment responses.

Case Presentation

A 63-year-old Chinese man presented with the major complaints of abdominal pain and fever for 3 days, in the absence of headache, dizziness, chest pain, dyspnoea, cough and sputum. The highest body temperature was 39.7°C. On physical examination, prominent signs were the urticaria-like skin lesions and the pan-abdominal tenderness. Complete blood count (CBC) showed the following: white blood cells (WBC), $19.13 \times 10^9/L$; neutrophils, $4.55 \times 10^9/L$; monocytes, $8.88 \times 10^9/L$; red blood cells (RBC), $2.38 \times 10^{12}/L$; hemoglobin (Hb), 80 g/L; platelets (Plt), $32 \times 10^9/L$; and reticulocytes (Ret), $5.61 \times 10^9/L$, C-reactive protein 142.7 mg/L. Coagulation profile and urine examination did not show any abnormalities. Biochemical analysis reported the elevated serum levels of lactate dehydrogenase (2834 IU/L), hydroxybutyric dehydrogenase (2394 IU/L) and $\beta 2$ -microglobulin (47.3 mg/L), in the absence of abnormalities in liver and renal functions. Pathogenic culture of his blood was sterile. Serologic tests for hepatitis A, B, C virus, and human immunodeficiency virus were negative. Biomarkers of neoplasms were negative too. No positive findings was presented in chest CT. However, abdominal CT scan revealed the swollen small and large intestines, abnormally accumulated airs in his small intestines, and lipotrophic lesions with overt angiogenesis surrounding the unusually thinned and distended small intestines and sigmoid colon, indicating the presence of gut inflammatory lesions (Fig. 1). Morphological examinations showed a heavily hypercellular bone marrow, with the significantly increased percentages of monoblasts (accounting for 44.5% of the total nucleated hematopoietic cells) and premonocytes (accounting for 24.5%). Increased percentages of premonocytes (44%) and monocytes (46%) were present on the blood smears (Fig. 2). Cytogenetic analysis reported a karyotype of 48,XY,t(8;21)(q22;q22),+13,+13[9]/49,idem,+mar[9]/49,idem,+8[2] (Fig. 3). Molecular biological analysis revealed the presence of a mutated *FLT3-TKD* gene and a fused *AML1-ETO* gene. Two groups of abnormal myeloid precursors were detected by flow cytometry. One group (accounting for 32.53% of the total nucleated cells) expressed CD13, CD33, CD14, CD11b, CD36, CD56, CD64, CD123 and HLA-DR; another group (accounting for 48.95% of the total nucleated cells) expressed CD34, CD117, CD38, HLA-DR, CD13, CD33, CD11b, CD56 and CD123. These data fulfilled the diagnostic criteria for AML-M4 with t(8;21)(q22;q22)/RUNX1-RUNX1T1 [1].

After admission, He was treated with piperacillin-tazobactam and etimicin for his febrile disease and dexamethasone for his urticaria-like skin lesions. He was also prescribed polyglycol electrolyte solution (1500 ml daily for 2 days) followed by rifaximin (200 mg four times daily) and berberine (0.3 g thrice times daily) in an attempt to quickly get rid of the pathogens and their metabolites in the intestines. The febrile episode and the urticaria-like skin lesions were quickly resolved. Surprisingly, the hematological profile gradually improved (CBC results in the following time are outlined in Fig. 4). On day 31, CBC

showed the following: WBC, $10.83 \times 10^9/L$; neutrophils, $6.24 \times 10^9/L$; monocytes, $1.62 \times 10^9/L$; RBC, $2.74 \times 10^{12}/L$; Hb, 93 g/L; Plt, $253 \times 10^9/L$; and Ret, $112.45 \times 10^9/L$. The absence of leukemia cells on blood smears indicated the loss of clonal growth advantage and an achievement of clinical hematological remission. He refused chemotherapy and hypomethylation therapy and was released. On day 51, he was admitted with the same symptoms as he was first admitted to our center. CBC and morphological examination of the blood smears confirmed the disease recurrence. Repeating the abovementioned treatment resulted in the second clinical and hematological responses. On day 105, he experienced the second recurrence, demonstrated resistance to antibiotic treatment and died of septic shock at another hospital.

Discussion And Conclusions

While acquisition of enhanced self-renewal capacity and impaired myeloid differentiation is the feature of acute leukemia, the emergence of symptomatic AML critically requires the acquisition of growth and survival advantage. Acquisition of enhanced self-renewal capacity results from the fused genes such as in recurrent chromosome arrangements and the mutated genes such as in transcription factor signaling pathways responsible for differentiation in certain lineage and certain stage of hematopoietic progenitors. Acquisition of clonal growth advantages results from the fused genes or mutated genes in growth receptors or their signaling pathways [1–3].

It is generally accepted that the constitutionally activated growth factor receptor signaling pathways are responsible for the growth and survival advantage in leukemic stem cells such as the formation of fused genes involving *ABL*, *FGFR1* and *PDGFR* and mutated genes involving *FLT3* and *KIT*, which result in the autonomous proliferation [1–3]. However, there may be another form of activating growth factor receptor signaling pathways in AML, ligand-dependent activation, like mutated genes in the B-cell receptor signaling pathway in lymphoma pathogenesis in which the antigen-dependent growth and survival advantages has been well elucidated [13–17]. In this setting, mutated genes in growth factor receptor signaling pathways may play a tonic role in intensifying the proliferative signaling after ligands binding to their receptors, and thereby acquiring the growth and survival advantage. Clonal B cells proliferate in response to antigen binding to B-cell receptors [13–17]; myeloid hematopoietic cells proliferate in response to ligands binding to pattern recognition receptors, cytokine receptors and colony stimulating factor receptors [18–22].

In our reporting case, the presence of increased percentages of blasts and CD 34 + progenitors in the bone marrow, the detection of chromosome arrangement of $t(8;21)(q22;q22)$ and fused *AML1-ETO* gene fulfilled the diagnosis of AML with recurrent chromosome arrangement of $t(8;21)(q22;q22)/RUNX1-RUNX1T1$. When admission, he presented with a febrile episode, overt gastrointestinal symptoms and urticaria-like skin lesions. In this setting, he was prescribed antibiotics to treat the febrile episode, dexamethasone to treat the urticaria-like skin lesions and a gut-cleansing preparation to quickly remove the gastrointestinal pathogens. Along with the relief of the gastrointestinal infections and the urticaria-like skin lesions, his hematological profile had been significantly improved. The absence of leukemia cells

on the blood smears suggested an achievement of clinical hematological remission. Because he refused chemotherapy and hypomethylation therapy, we had the opportunity to observe the recapitulated treatment response. These recapitulated treatment responses suggested that altered inflammatory stresses contributed to the loss of clonal growth and survival advantage, in support of a ligand-dependent clonal growth advantage. This ligand could be intestine-derived pathogen-associated molecular pattern, cytokine or colony stimulating factor produced in response to infectious offending [18–22]. After the second relapse, he demonstrated resistance to antibiotic and glucocorticoid treatment and died of septic shock probably due to the acquisition of a new pathogenic infection like our previously reported case [23]

Taken together, the recapitulated antibiotic and glucocorticoid treatment-induced hematological remissions strongly indicated a ligand-dependent growth advantage in AML emergence. This phenomenon warrants further investigations and may be helpful in improving therapeutic outcome in a subgroup of AML.

Abbreviations

AML: acute myeloid leukemia; CBC: complete blood count; WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin; Plt: platelets; Ret: reticulocytes; CT, computerized tomography;

Declarations

Ethics approval: Approval was granted by the Ethics Committee of The Central Hospital of Qingdao West Coast New Area.

Consent to participate: Written informed consent was obtained from the patients' son.

Consent for publication: Written informed consent was obtained from the patient' son for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Authors' contributions: XYS and X CZ developed the idea, XYS, XQY, and XDY participated in treating the patients and collected the data, XYS and SXX analyzed the data and wrote the manuscript, FJM and X CZ

supervised the treatment and revised the manuscript, XCZ decided and approved the final version. All authors read and approved the final manuscript.

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References

1. Liesveld JL and Lichtman MA. Acute myelogenous leukemia. In: Kaushansky K, Prchal JT, Press OW, Lichtman MA, Levi M, Burns LJ, Caligiuri MA, editors. Williams Hematology, 9th edn. McGraw-Hill, New York; 2016. p. 1373-1436.
2. Kishtagari A, Levine RL. The Role of Somatic Mutations in Acute Myeloid Leukemia Pathogenesis. *Cold Spring Harb Perspect Med.* 2021;**11**:a034975. doi: 10.1101/cshperspect.a034975. PMID: 32398288. PMCID: PMC8015698.
3. Higgins A, Shah MV. Genetic and Genomic Landscape of Secondary and Therapy-Related Acute Myeloid Leukemia. *Genes (Basel).* 2020;**11**:749. doi: 10.3390/genes11070749. PMID: 32640569. PMCID: PMC7397259.
4. Rashidi A, Fisher SI. Spontaneous remission of acute myeloid leukemia. *Leuk Lymphoma.* 2015;**56**:1727-1734. doi: 10.3109/10428194.2014.970545. PMID: 25284494.
5. Teng CJ, Yang CF, Gau JP, Liu JH, Hong YC, Liu CY, Yu YB, Hsiao LT, Wang WS, Tzeng CH. Spontaneous remission in acute myelogenous leukemia evidenced by cytogenetic changes. *Ann Hematol.* 2011;**90**:981-983. doi: 10.1007/s00277-010-1120-0. PMID: 21107840.
6. Zeng Q, Yuan Y, Li P, Chen T. Spontaneous remission in patients with acute myeloid leukemia with t(8;21) or cutaneous myeloid sarcoma: two case reports and a review of the literature. *Intern Med.* 2013;**52**:1227-1233. doi: 10.2169/internalmedicine.52.9505. PMID: 23728561.
7. Gyárfás T, Wintgens J, Biskup W, Oschlies I, Klapper W, Siebert R, Bens S, Haferlach C, Meisel R, Kuhlen M, Borkhardt A. Transient spontaneous remission in congenital MLL-AF10 rearranged acute myeloid leukemia presenting with cardiorespiratory failure and meconium ileus. *Mol Cell Pediatr.* 2016;**3**:30. doi: 10.1186/s40348-016-0061-7. PMID: 27510896; PMCID: PMC5002396.
8. Hoshino T, Taki T, Takada S, Hatsumi N, Sakura T. Spontaneous remission of adult acute myeloid leukemia with t(8;16)(p11;p13)/MOZ-CBP fusion. *Leuk Lymphoma* 2018;**59**:253-255. doi: 10.1080/10428194.2017.1320712. PMID: 28535725.
9. Camus V, Etancelin P, Jardin F, Lenain P, Contentin N, Daliphard S, Buchonnet G, Lemasle E, Lanic H, Leprêtre S, Penther D, Dubois S, Tilly H, Bastard C, Stamatoullas A. Spontaneous remission in three cases of AML M5 with NPM1 mutation. *Clin Case Rep.* 2015;**3**:955-9. doi: 10.1002/ccr3.408. PMID: 26576281. PMCID: PMC4641483.
10. Khalife-Hachem S, Pegliasco J, Saada V, Hernandez E, Camara-Clayette V, Cotteret S, Benabdelali R, de Botton S, Marzac C, Micol JB. Spontaneous molecular response of IDH2 acute myeloid leukemia. *Ann Hematol.* 2020;**99**:353-354. doi: 10.1007/s00277-019-03876-8. PMID: 31814054.

11. Mozafari R, Moeinian M, Asadollahi-Amin A. Spontaneous Complete Remission in a Patient with Acute Myeloid Leukemia and Severe Sepsis. *Case Rep Hematol*. 2017;**2017**:9593750. doi: 10.1155/2017/9593750. PMID: 28811942. PMCID: PMC5546120.
12. Maywald O, Buchheidt D, Bergmann J, Schoch C, Ludwig WD, Reiter A, Hastka J, Lengfelder E, Hehlmann R. Spontaneous remission in adult acute myeloid leukemia in association with systemic bacterial infection-case report and review of the literature. *Ann Hematol*. 2004;**83**:189-194. doi: 10.1007/s00277-003-0741-y. PMID: 15064869.
13. Thurner L, Hartmann S, Neumann F, Hoth M, Stilgenbauer S, Küppers R, Preuss KD, Bewarder M. Role of Specific B-Cell Receptor Antigens in Lymphomagenesis. *Front Oncol*. 2020;**10**:604685. doi: 0.3389/fonc.2020.604685. PMID: 33363034. PMCID: PMC7756126.
14. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;**17**:57. doi:10.1186/s12943-018-0779-z. PMID: 29455639. PMCID: PMC5817726.
15. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. *Blood*. 2011;**117**:1792-8. doi: 10.1182/blood-2010-06-275818. PMID: 20959600.
16. Mueller A, O'rourke J, Chu P, Chu A, Dixon MF, Bouley DM, Lee A, Falkow S. The role of antigenic drive and tumor-infiltrating accessory cells in the pathogenesis of helicobacter-induced mucosa-associated lymphoid tissue lymphoma. *Am J Pathol*. 2005;**167**:797-812. doi: 10.1016/S0002-9440(10)62052-4. PMID: 16127158. PMCID: PMC1698723.
17. Hoogeboom R, van Kessel KP, Hochstenbach F, Wormhoudt TA, Reinten RJ, Wagner K, Kater AP, Guikema JE, Bende RJ, van Noesel CJ. A mutated B cell chronic lymphocytic leukemia subset that recognizes and responds to fungi. *J Exp Med*. 2013;**210**:59-70. doi: 10.1084/jem.20121801. PMID: 23296468. PMCID: PMC3549718.
18. Nagai Y, Garrett KP, Ohta S, Bahrn U, Kouro T, Akira S, Takatsu K, Kincade PW. Toll-like receptors on hematopoietic progenitor cells stimulate innate immune system replenishment. *Immunity*. 2006;**24**:801-812. doi: 10.1016/j.immuni.2006.04.008. PMID: 16782035. PMCID: PMC1626529.
19. Chiba Y, Mizoguchi I, Hasegawa H, Ohashi M, Orii N, Nagai T, Sugahara M, Miyamoto Y, Xu M, Owaki T, Yoshimoto T. Regulation of myelopoiesis by proinflammatory cytokines in infectious diseases. *Cell Mol Life Sci*. 2018;**75**:1363-1376. doi: 10.1007/s00018-017-2724-5. PMID: 29218601.
20. Mitroulis I, Kalafati L, Bornhäuser M, Hajishengallis G, Chavakis T. Regulation of the Bone Marrow Niche by Inflammation. *Front Immunol*. 2020;**11**:1540. doi: 10.3389/fimmu.2020.01540. PMID: 32849521. PMCID: PMC7396603.
21. Paracatu LC, Schuettpeitz LG. Contribution of Aberrant Toll Like Receptor Signaling to the Pathogenesis of Myelodysplastic Syndromes. *Front Immunol*. 2020;**11**:1236. doi: 10.3389/fimmu.2020.01236. PMID: 32625214. PMCID: PMC7313547.
22. Karimdadi Sariani O, Eghbalpour S, Kazemi E, Rafiei Buzhani K, Zaker F. Pathogenic and therapeutic roles of cytokines in acute myeloid leukemia. *Cytokine*. 2021;**142**:155508. doi: 10.1016/j.cyto.2021.155508. PMID: 33810945.

23. Zhao XC, Sun XY, Ju B, Meng FJ, Zhao HG. Acquired aplastic anemia: Is bystander insult to autologous hematopoiesis driven by immune surveillance against malignant cells? *World J Stem Cells*. 2020;**12**:1429-1438. doi: 10.4252/wjsc.v12.i11.1429. PMID: 33312408. PMCID: PMC7705466.

Figures

Figure 1

Abdominal CT imaging of the patient: abnormally accumulated airs in the small intestines (marked by yellow arrows); significantly thickened and air-filled distal ileum (marked by black arrows), markedly thickened descending colon (marked by red arrows) and lipotrophic lesions with overt angiogenesis

surrounding the unusually thinned and distended small intestines (marked by yellow arrows) and sigmoid colon (marked by a purple arrow).

Figure 2

Morphological evaluation of the bone marrow and peripheral blood smears. A: a heavily hypercellular bone marrow with the increased percentages of monoblasts (accounting for 44.5% of the total nucleated hematopoietic cells) and premonocytes (accounting for 24.5%). B: Increased percentages of premonocytes (accounting for 44%) and monocytes (accounting for 46%).

Figure 3

Cytogenetic analysis for the bone marrow culture: Cytogenetic analysis reported a karyotype of 48,XY,t(8;21)(q22;q22),+13,+13[9]/49,idem,+mar[9]/49,idem,+8[2].

Hematological response to antibiotic and dexamethasone treatment

Figure 4

Hematological responses following antibiotic and dexamethasone treatment: Following antibiotic and dexamethasone treatment, the white blood cells (WBC, $\times 10^9/L$) and monocytes (Mon, $\times 10^9/L$) gradually decreased, and the neutrophils (Neu, $\times 10^9/L$), hemoglobin (Hb, $\times 10\text{ g/L}$), platelets (Plt, $\times 10 \times 10^9/L$) and reticulocytes (Ret, $\times 10 \times 10^9/L$) gradually increased. The patient rapidly relapsed due to the discontinuation of antibiotic and dexamethasone treatment. After relapse, repeating the same treatment resulted in the recapitulated hematological response.