

World Journal of *Stem Cells*

World J Stem Cells 2020 November 26; 12(11): 1237-1438



REVIEW

- 1237 Role of platelets and breast cancer stem cells in metastasis
Mendoza-Almanza G, Burciaga-Hernández L, Maldonado V, Melendez-Zajgla J, Olmos J
- 1255 Understanding cellular and molecular mechanisms of pathogenesis of diabetic tendinopathy
Lu PP, Chen MH, Dai GC, Li YJ, Shi L, Rui YF
- 1276 Multifunctional role of microRNAs in mesenchymal stem cell-derived exosomes in treatment of diseases
Xu HK, Chen LJ, Zhou SN, Li YF, Xiang C
- 1295 Advance in metabolism and target therapy in breast cancer stem cells
Gao X, Dong QZ
- 1307 Stem cell quiescence and its clinical relevance
Luo M, Li JF, Yang Q, Zhang K, Wang ZW, Zheng S, Zhou JJ
- 1327 New insight into dental epithelial stem cells: Identification, regulation, and function in tooth homeostasis and repair
Gan L, Liu Y, Cui DX, Pan Y, Wan M

MINIREVIEWS

- 1341 Isolation and characterization of mesenchymal stem cells in orthopaedics and the emergence of compact bone mesenchymal stem cells as a promising surgical adjunct
Anastasio A, Gergues M, Lebhar MS, Rameshwar P, Fernandez-Moure J

ORIGINAL ARTICLE

Basic Study

- 1354 AlCl₃ exposure regulates neuronal development by modulating DNA modification
Cheng XJ, Guan FL, Li Q, Dai G, Li HF, Li XK
- 1366 Application of cattle placental stem cells for treating ovarian follicular cyst
Peng SY, Wu TH, Lin TY, Hii LY, Chan KS, Fu TY, Chang SC, Shen PC, Liu KY, Shaw SW
- 1377 Immunophenotypic characteristics of multipotent mesenchymal stromal cells that affect the efficacy of their use in the prevention of acute graft vs host disease
Petinati N, Kapranov N, Davydova Y, Bigildeev A, Pshenichnikova O, Karpenko D, Drize N, Kuzmina L, Parovichnikova E, Savchenko V
- 1396 Effect of conditioned medium from neural stem cells on glioma progression and its protein expression profile analysis
Zhang GL, Qian C, Zhang SZ, Tuo YH, Zeng BY, Ji YX, Wang YZ

- 1410** Glutathione metabolism is essential for self-renewal and chemoresistance of pancreatic cancer stem cells
Jagust P, Alcalá S, Sainz Jr B, Heeschen C, Sancho P

LETTER TO THE EDITOR

- 1429** Acquired aplastic anemia: Is bystander insult to autologous hematopoiesis driven by immune surveillance against malignant cells?
Zhao XC, Sun XY, Ju B, Meng FJ, Zhao HG

ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Dr. Alessandra Pelagalli is a Senior Researcher of veterinary physiology in the Department of Advanced Biomedical Sciences at the University of Naples. Having completed her Pharmacy Degree from the University of Naples in 1991, Dr. Pelagalli continued her postgraduate training and received her PhD in 1996. She became a Young Researcher at the University of Naples in 1999, working in animal platelet physiology and biochemistry. Her current research interests and publications focus on the roles and behavior of bone marrow mesenchymal stem cells in the differentiation processes after stimulation, water channel proteins in cell migration, and aquaporins in various tissues, such as gut and the male reproductive tract. (L-Editor: Filipodia)

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The *WJSC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, BIOSIS Previews, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJSC* as 3.231; IF without journal self cites: 3.128; Ranking: 18 among 29 journals in cell and tissue engineering; Quartile category: Q3; Ranking: 113 among 195 journals in cell biology; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yun-Xiaojian Wu; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Stem Cells

ISSN

ISSN 1948-0210 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shengwen Calvin Li, PhD, MPhil., FRSM, Tong Cao, Carlo Ventura

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

PUBLICATION DATE

November 26, 2020

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INSTRUCTIONS TO AUTHORS

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<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Acquired aplastic anemia: Is bystander insult to autologous hematopoiesis driven by immune surveillance against malignant cells?

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Author contributions: Zhao XC, Sun XY, and Ju B performed the research work, analyzed the data, and drafted the manuscript; Meng FJ and Zhao HG supervised the treatment and revised the manuscript; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

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Abstract

We previously reported a serendipitous finding from a patient with refractory severe aplastic anemia who had gotten an unexpected hematological response to treatment with gut-cleansing preparations (GCPs). This patient experienced three recurrences over the ensuing one year of intermittent GCP treatments, with each recurrence occurring 7-8 wk from a GCP. After his third recurrence, he was prescribed successive treatment with rifampicin, berberine, and monthly administered GCP for 4 mo, and he developed an erythroid proliferative neoplasia and an overwhelming enteropathy, and eventually died of septic shock. Laboratory investigations had validated the resolution of myelosuppression and the appearance of malignant clonal hematopoiesis. From the treatment process and laboratory investigations, it is reasonably inferred that the engagement of gut inflammation is critically required in sustaining the overall pathophysiology of acquired aplastic anemia probably by creating a chronic inflammatory state. Incorporation of rifampicin, berberine, and monthly GCP into cyclosporine can enhance the immunosuppressive effect. In a subgroup of acquired aplastic anemia patients whose pathogenesis is associated with genotoxic exposure, the suppressed normal hematopoiesis may result from the bystander insult that is mediated by the soluble inflammatory cytokines generated in response to the immunogenic products of damaged hematopoietic cells in the context of chronic inflammatory state and may offer a protective antineoplastic mechanism against malignant proliferation.

Key Words: Acquired aplastic anemia; Bystander insult; Malignant clonal hematopoiesis; Immune surveillance; Antineoplastic; Gut inflammation

Manuscript source: Unsolicited manuscript

Specialty type: Cell and tissue engineering

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

Received: February 14, 2020

Peer-review started: February 14, 2020

First decision: September 11, 2020

Revised: September 20, 2020

Accepted: September 25, 2020

Article in press: September 25, 2020

Published online: November 26, 2020

P-Reviewer: Avtanski D, Demonacos C, Xavier-Elsas P

S-Editor: Zhang L

L-Editor: Wang TQ

P-Editor: Li JH



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Core Tip: We previously reported a severe aplastic anemia patient who had gotten an unexpected hematological response to treatment with intermittent gut-cleansing preparations. After his third recurrence, he was prescribed successive treatment with rifampicin, berberine, and monthly administered gut-cleansing preparations for 4 mo, and he developed an erythroid proliferative neoplasia and an overwhelming enteropathy. We hereby make an extrapolation that, in a subgroup of aplastic anemia patients, the suppressed normal hematopoiesis may result from the bystander insult that is generated in response to the antigenic products of damaged hematopoietic cells, and may offer a protective antineoplastic mechanism against malignant proliferation.

Citation: 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(11): 1429-1438

URL: <https://www.wjgnet.com/1948-0210/full/v12/i11/1429.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v12.i11.1429>

TO THE EDITOR

Acquired aplastic anemia (AAA) has been generally accepted as the paradigm of immune-mediated bone marrow failure syndrome, in which the antigen-driven and abnormally activated cellular immune responses trigger the destructive attack on hematopoietic stem and progenitor cells (HSPCs) in genetically susceptible individuals. An inappropriately enhanced inhibitory and pro-apoptotic capacity of these deranged immune reactions to HSPCs from highly sensitized "autoreactive" cytotoxic T lymphocytes (CTLs) by targeting against yet unidentified antigens is responsible for the overall pathophysiology. The significantly increased intramedullary death of HSPCs results in markedly hypocellular bone marrow (BM) and varying degrees of periphery pancytopenia^[1-3]. Overproduction of soluble proinflammatory mediators by phenotypically and functionally skewed CTLs, mainly through expressing and secreting high levels of interferon- γ (IFN- γ) and tumor necrosis factor - α (TNF- α), with an IFN- γ predominance, is the distinctive immunological feature. It is the inflammatory cytokines that upregulate the expression of pattern recognition receptors, antigen-presenting and apoptosis-associated molecules on hematopoietic precursors, and exert the direct detrimental effect on normal hematopoiesis in a manner resembling bystander effect^[4-6]. A large number of infectious and genotoxic agents have been implicated as the culprit in this chronic inflammatory process^[1,2]. However, little is known about what the immunogenic substances are and where the driving force comes to sustain the high responsiveness of these CTLs. Given the vast diversity of implicated offending agents that have been reported to be associated with AAA pathogenesis, the protean presentation in disease severity and comorbidities, the variable therapeutic responses to immunosuppressive therapies (ISTs), the differential prognosis with regard to disease persistence and progression^[1-3], and the great complexity of possible mechanisms that are involved in driving autoimmune diseases^[7-9], AAA may be a heterogenous entity, and the bone marrow suppression (BMS) in AAA is most likely to be a consequence of different priming and sustaining mechanisms in different risk genetic backgrounds in response to different hostile environmental challenges converging upon, irrespective of varying degrees of myelosuppression, the same phenotypically immunological destructive effect on HSPCs. Recently, much like in other autoimmune diseases^[10], the driving force behind the initiation, development, chronicity, and progression of AAA pathophysiology has been proposed to come from the altered composition of gut microbiota and the compromised integrity of the intestinal barrier^[11-13]. On the other hand, the overlapping spectrum in clinical and morphological features, immunological profile, genetic abnormalities, and therapeutic responses to ISTs between AAA and hypoplastic myelodysplastic syndrome (hMDS, probably also encompassing a subgroup of low risk MDS)^[14-19], as well as the occurrence of malignant clonal hematopoiesis (MCH) in approximately 10%-15% of AAA patients who had accepted successful ISTs^[20] strongly indicates that, at least in a subgroup of AAA patients, the

seemingly pathogenic BMS may directly target against the neo-antigens on genetically damaged hematopoietic precursors and may offer a possible protective role: Antineoplastic mechanism against malignant proliferation^[21,22]. The emergence of MCH in a patient with refractory severe aplastic anemia (RSAA) following the resolution of BMS by treatment of his gut inflammatory disease with GCP provides indirect but forceful information in support of this extrapolation.

We previously reported a serendipitous finding from a 30-year-old RSAA man who had gotten an unexpected hematological response to treatment of gut inflammatory condition (GIC)^[23]. Having a 23-year history of AAA and two relapses, this patient, with relapses and with age, gradually lost the therapeutic response to cyclosporine (CsA), stanozolol, rhG-CSF (recombinant human granulocyte colony-stimulating factor), and eltrombopag treatment, which worsened and accelerated the impairment of already severely reduced hematopoietic capacity. The particularly noteworthy event was the dimethylbenzene exposure due to his house being decorated 8 mo before the disease onset. From March to June 2018, he experienced a 3-mo-long episode of agnogenic febrile disease, and intensive treatment with many kinds of intravenously delivered broad-spectrum antibiotics failed to settle the inflammatory episode. When presenting with abdominal cramps, he accepted orally administered mannitol and gentamycin treatment. This GCP treatment not only resulted in a quick settlement of his fever but also produced an unexpectedly good hematological response. He underwent three recurrences over the ensuing one year of intermittent GCP treatments, with each recurrence occurring 7-8 wk from a GCP. However, subsequent GCP treatment was capable of inducing subsequent remission, and consecutive GCP treatments successfully yielded prolonged hematological improvement, confirming the definitive contribution of GIC to AAA pathophysiology.

Given the eubiotic properties of rifamycin and berberine^[24,25], this patient was prescribed successive administration of rifampicin (450 mg, once per day) and berberine (0.3 g, thrice per day) with monthly administered GCP (1500 mL polyethylene glycol electrolyte solution per day for 2 d) after his third recurrence. Other employed drugs included lactulose oral solution (45-50 mL per day), inulin (15-20 g per day), and probiotics consisting of *Lactobacillus acidophilus*, *Clostridium butyricum*, *Bifidobacterium*, *Bacillus coagulans*, and *Enterococcus*. Regularly used drugs (including CsA 125 mg, twice per day; stanozolol 2 mg, thrice per day; eltrombopag 25 mg, once per day; and rhG-CSF 100 µg, twice per day) went on to be delivered at the same dose as before. With the achievement of a rapid increase in white blood cell count (WBC), rhG-CSF was tapered off. These treatments had arrived successfully at a steady hematological improvement, with normal levels of WBC, hemoglobin (Hb), and platelet count (Plt).

Unfortunately, a steep drop in WBC, Hb, and Plt occurred 4 mo later. On admission, his major complaints were “rapidly aggravated dizziness, fatigue, pallor, and anxiety for 1 wk, and abdominal distension and cramps for 3 d”, in the absence of fever, chills, cough, and expectoration. Upon physical examination, major signs were bruise-looking appearance and abdominal tenderness. Routine blood tests showed the following: WBC, 2600/µL; absolute neutrophil count, 980/µL; red blood cell count, 2560000/µL; Hb, 5.9 g/dL; Plt, 7000/µL; absolute reticulocyte count, 137600/µL; and C-reactive protein, 62.42 mg/L. Examination of the coagulation profile was within normal limits, with a D-dimer of 0.69 mg/L. Biochemical tests showed elevated serum levels of uric acid, urea nitrogen, glucose, potassium, and β2-microglobulin, and reduced serum levels of globulin, sodium, and calcium (Table 1). A reduced serum level of complement component-3 was detected. Computerized tomography examination of the abdomen revealed hepatosplenomegaly (Figure 1A and B) as well as an adynamic ileus and the thickened walls of terminal ileum, ascending, and sigmoid colon (Figure 1C and D). Morphological evaluation of the BM showed a strikingly increased percentage of nucleated erythrocytes that account for 80.5% (with some of them displaying the dysplastic features) of the total nucleated cells, with a markedly reduced percentage of myeloid precursors and lymphocytes (Table 1 and Figure 2A and B). A substantial percentage of nucleated erythrocytes were presented on peripheral blood smears, in the presence of marked morphological abnormalities of anisocytosis, acanthocytes, and schistocytes in mature erythrocytes (Table 1 and Figure 2C and D). Flow cytometric analysis for the BM revealed a pronounced increase in the percentage of CD45⁺ cells and CD71⁺ cells as well as a relatively increased percentage of CD8⁺ cells and CD33⁺ cells, and a markedly decreased percentage of CD4⁺ cells and CD19⁺ cells, without an increase in CD34⁺ cells and CD117⁺ cells, indicating an erythroid commitment and CD8⁺ cytotoxic T cell predominance (Table 1 and Supplementary Figure 1). CD55 and CD59 expression was within the normal levels. Cytogenetic analysis by culturing the BM sample reported a karyotype of

Table 1 Major laboratory results for the investigation of this patient

Specific results
Complete blood count
WBC, 2600/ μ L; ANC, 980/ μ L; RBC, 2560000/ μ L; Hb, 5.9 g/dL; Plt, 7000/ μ L; Ret, 137600/ μ L, CRP, 62.42 mg/L
Coagulation profile
APTT, 38.4 s; PT, 12.6 s; TT, 17.7 s; Fig, 2.56 g/L; DD 0.69 mg/L
Abnormalities in biochemical tests
Elevated serum levels of: Uric acid, 8.52 mg/dL; Urea nitrogen, 26.04 mg/dL; Glucose, 418.68 mg/dL; Potassium, 23.44 mg/dL; β 2-microglobulin, 4.58 mg/L; Reduced serum levels of: Albumin, 33.1g/L; Globulin, 18.1 g/L; Sodium, 3.10 mg/dL; Calcium, 8.24 mg/dL; Carbon dioxide, 19.3 mmol/L
Complements
C3, 0.62 g/L; C4, 0.11 g/L
Germcultures of the blood
Positive result for <i>Candida albicans</i> ; Negative results for aerobic and anaerobic bacteria
Morphological evaluation of the BM and PB smears
BM: Promyelocytes, 0.5%; Myelocytes, 1.5%; Metagranulocytes, 2.5%; Stab cells, 3.0%; Segmented granulocytes, 1.5%; Eosinophilic granulocytes, 0.5%; Early erythroblasts, 3.5%; Intermediate erythroblasts, 15.0%; Late erythroblasts, 62.0%; Lymphocytes, 9.5%; Monocytes, 0.5%; PB: Metagranulocytes, 4.0%; Stab cells 18.0%; Segmented granulocytes, 7.0%; Early erythroblasts, 2%; Intermediate erythroblasts, 11%; Late erythroblasts, 49%; Lymphocytes, 9.0%
Flow cytometric analysis for the BM specimen
CD45-, 48.30%; CD45-CD71+, 35.68%; CD34, 2.16%; CD117, 6.86%; HLA-DR, 16.74%; CD34+CD117+, 1.59%; CD34+HLA-DR+, 1.06%; CD13, 39.42%; CD33, 36.4%; CD11b, 40.57%; CD16, 24.96%; CD14, 5.52%; CD64, 23.22%; CD13+CD16+, 24.34%; CD15+CD11b+, 29.38%; CD3, 11.71%; CD2, 7.39%; CD4, 9.72%; CD8, 15.78%; CD5, 5.36%; CD7, 5.25%; CD56, 10.63%; CD3+CD2+, 5.57%; CD3+CD4+, 4.57%; CD3+CD8+, 6.97%; CD3+CD5+, 5.24%; CD3+CD56+, 1.02%; CD3+CD7+, 4.22%; CD19, 2.19%; CD19+CD20+, 1.57%; CD19+CD10+, 0.14%; CD19+CD5+, 0.12%; CD19+CD38+, 0.13%
PHN clone analysis
Red blood cells: CD55, 99.69%; CD59, 99.51%; Granulocytes: CD55, 98.03%; CD59, 96.30%
Conventional cytogenetic analysis
45,XY,-7[10]
Genetic investigations for hematopoietic malignancy
Positive results for KRAS, 44.2%; RUNX1, 43.8%; PTPN11, 45.4%; SETBP1, 49.5%; Negative results for GNAS, NRAS, HRAS, ASXL1, EZH2, DNMT3A, TET2, SF3B1, SRSF2, U2AF1, ZRSR2, STAG2, CBL, CBLB, CBLC, CUX1, ETV6, GATA2, IDH1, IDH2, JAK2, MPL, CALR, NOTCH1, WT1, TP53

WBC: White blood cell count; Hb: Hemoglobin level; Plt: Platelet count; BM: Bone marrow; PB: Periphery blood.

45,XY,-7[10], confirming the presence of clonal hematopoiesis. Gene mutations in *KRAS*, *RUNX1*, *PTPN11*, and *SETBP1* were identified. These above-mentioned data met the criteria for diagnosis of an erythroid proliferative neoplasma with dysplastic features, but it cannot be categorized precisely into any kind of World Health Organization classification of myeloid neoplasms and acute leukemia^[26]. A reduced ratio of CD4+/CD8+ cells confirmed the CD8+ CTL-predominated immune responses in excellent concordance with the characteristic immunological profile in AAA^[1,2] and other cellular immune-mediated autoimmune diseases, while an increased percentage of CD3+CD5+ cells reinforced the autoimmune nature. An enhanced ratio of CD33+/CD19+ cells and increased percentages of CD14+ cells and CD3-CD56+ cells reflected a bias of the homeostatic hematopoiesis towards innate immune responses against ongoing infections^[27,28]. The patient exhibited strong resistance to intravenous antibiotic and glucocorticosteroid treatments, developed an overwhelming enteropathy and systemic inflammatory response syndrome with rapid progression to multiorgan dysfunction, and eventually died of septic shock. Germcultures of the blood reported a positive result for *Candida albicans* and negative results for aerobic and anaerobic bacteria in the lag period.

From the treatment process and laboratory investigations of this reported case, it is reasonably inferred that: (1) Engagement of GIC is critically required in the sustenance of overall pathophysiology in AAA; (2) Incorporation of rifampicin, berberine, and monthly GCP treatments into CsA can enhance the sensitivity of immunosuppressive agents; and (3) In a subgroup of AAA patients, the suppressed normal hematopoiesis may result from the bystander insult that is mediated by the soluble inflammatory

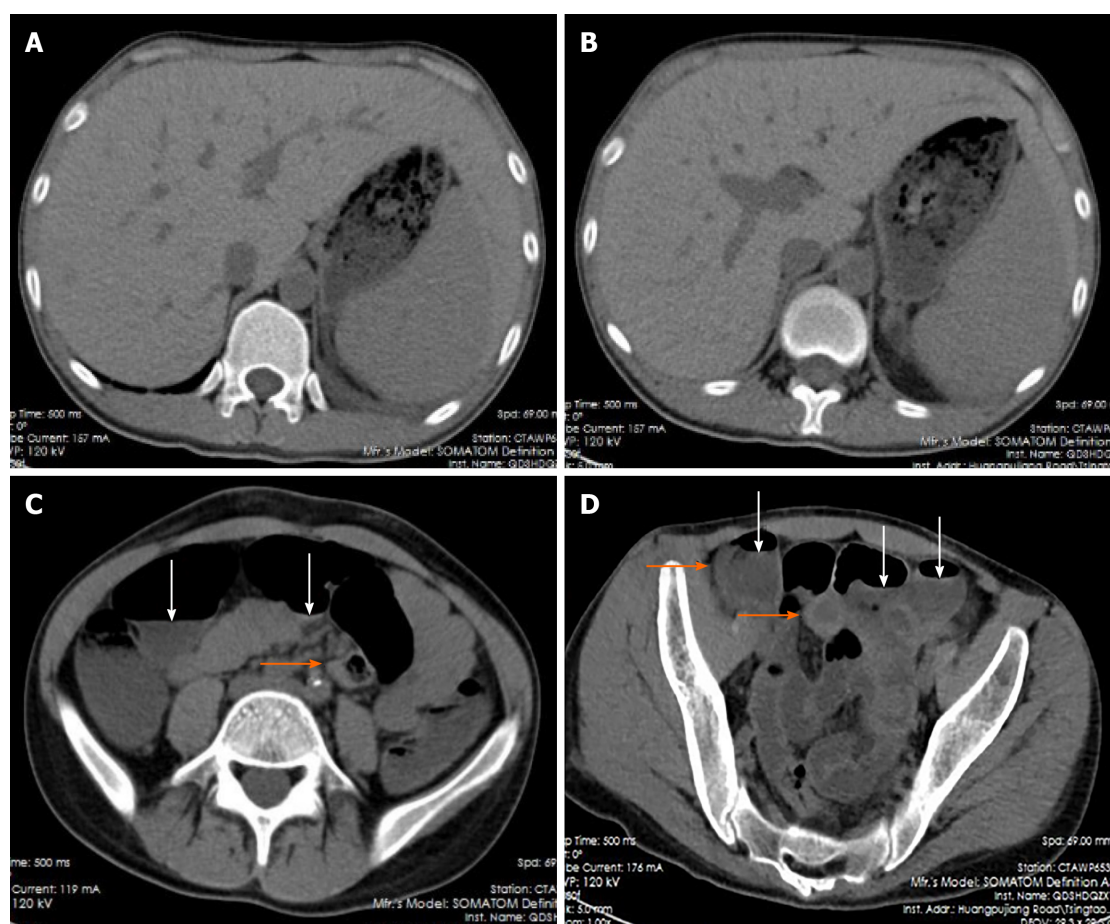


Figure 1 Computerized tomography examination of the abdomen. A and B: Computerized tomography examination of the upper abdomen reported an enlarged liver and an enlarged spleen; C and D: Computerized tomography examination of the intermediate and low abdomen displayed the increased fluids and multiple liquid gas interfaces in the intestinal lumen (marked by white arrows) as well as the thickened walls of terminal ileum, ascending, and sigmoid colon (marked by orange arrows), in accordance with the diagnosis of an adynamic ileus and colonitis that provides evidence for the presence of gut inflammatory disease.

cytokines generated in response to the immunogenic products of damaged HSPCs in the context of chronic inflammatory condition and may offer a protective antineoplastic mechanism against malignant proliferation. The finding that the combination of rifampicin, berberine, and monthly GCP with CsA was able to produce good hematological responses strongly indicates the definitive contribution of dysbiotic gut microbiota to the maintenance of chronic and progressive bone marrow failure syndrome^[11,13,23]. The contribution of gut microbiota to the immune-mediated pathophysiology has also been corroborated in the induction of chronic graft-*vs*-host disease by transfusion of allogeneic HSPCs into semi-lethally irradiated mice^[29], a pathogenic process resembling that of AAA and being broadly used as animal models to study AAA pathogenesis^[30]. The role of GIC in triggering the onset, development, and progression of autoimmune diseases may act as an intensifier that links the host immunogenetics with environmental challenges to augment the already dysregulated autoimmunity^[31] and may promote the establishment of an inflammatory state by innate immune cells sensing pathogen-associated molecular patterns on commensal microbes^[32,33], which most likely produces an adjuvant effect to break down the host immune homeostasis and to perpetuate the high responsiveness of specific antigen-primed CTLs^[34,35]. It should not be surprising that GICs play such an essential role in the sustenance of AAA pathophysiology because human gastrointestinal tract not only is the largest and most vulnerable interface that links the host psycho-neuro-endocrino-immune system with detrimental environmental factors but also represents the most enriched gut-associated lymphatic tissue and resides the most complex microbial community that play an essential role in the development, education, and maturation of host immune system, and shape the host immune responses to infections and various injuries^[36,37]. Impaired intestinal barrier in structure, integrity, and function allows the intestinally derived antigens to penetrate the intestinal epithelium and intrude into the lamina propria, blood, and BM^[38], which likely plays pivotal roles in sustaining the unwanted autoimmunity by persistent exposure of host

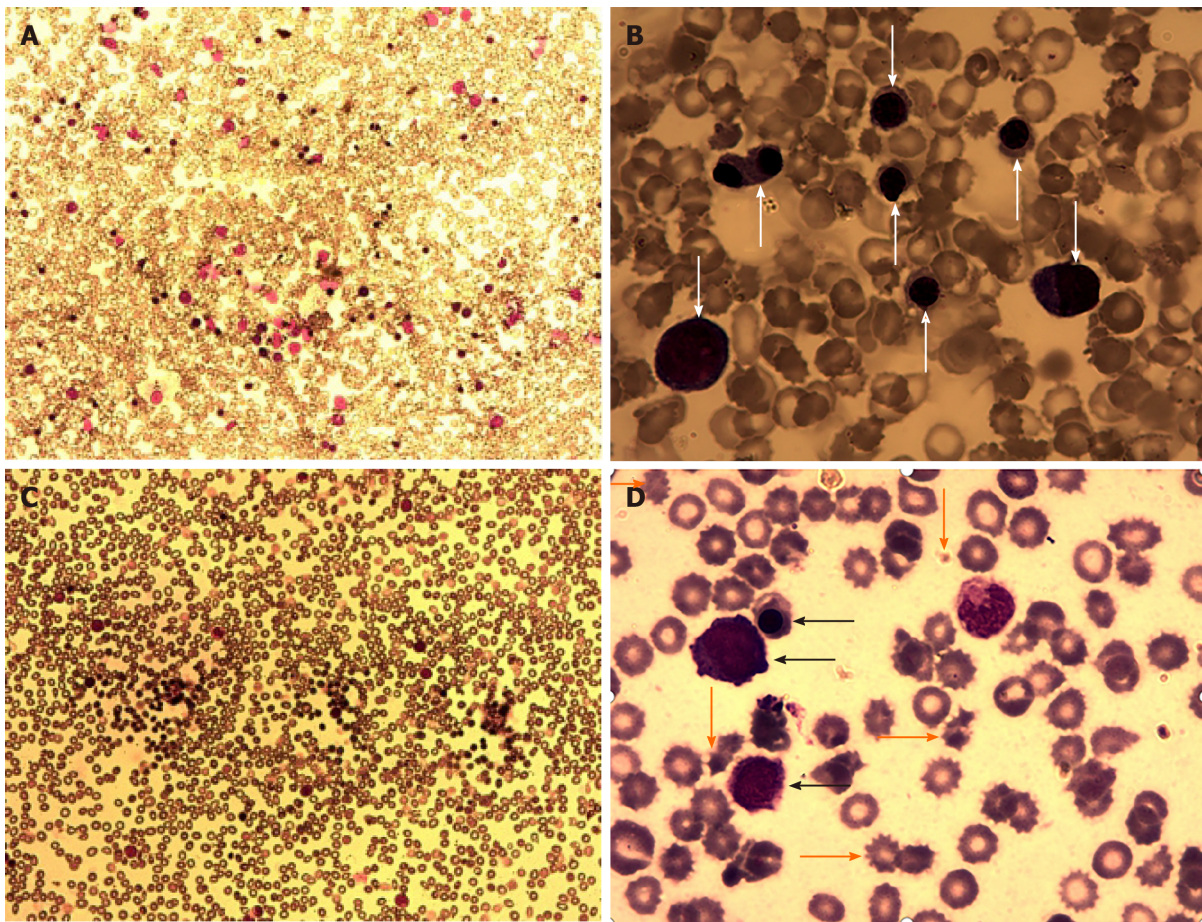


Figure 2 Morphological examination of bone marrow and periphery blood smears. A: Morphological examination of bone marrow (BM) smears under low power lens (10×10) showed a normal cellularity, in the absence of fatty replacement; B: Morphological enumeration of BM nucleated cells under high power lens (10×100) showed an increased percentage of nucleated erythrocytes in multiple stages (marked by white arrows), with markedly reduced percentages of myeloid precursors and lymphocytes; C: Morphological examination of periphery blood (PB) smears under low power lens (10×10) showed an increase in nucleated cells, predominantly nucleated erythrocytes; D: Morphological enumeration of PB nucleated cells under high power lens (10×100) showed the presence of nucleated erythrocytes in multiple stages (marked by black arrows), with marked anisocytosis, acanthocyte, and schistocyte in mature erythrocytes (marked by orange arrows). The morphological features of the BM and PB fulfilled the diagnosis of an erythroid proliferative disease and the toxic damage of erythrocytes.

innate and adaptive immune cells to the exogenous antigens from gut commensal microbes. In contrast to several recurrences earlier, successive administration of rifampicin and berberine with monthly GCP enhanced the immunosuppressive effect of CsA probably due to the reduced gut-derived stimulation that leads to the mitigated adjuvant effect. However, this patient still developed an overwhelming enteropathy in the course of eubiotic treatment, suggesting the appearance of a new dysbiosis in the gut microbial ecology in which the pathogens were resistant to rifamycin and berberine treatment. The absence of respiratory system symptoms and signs indicated that the *Candida albicans* in blood most likely came from the intestines. The increase in reticulocyte count, the presence of normal cellularity, and the absence of fatty replacement on the BM smears gave the strong evidence to make us to believe with certainty that the previously existing myelosuppressive state had already been resolved, and the *Candida* infection is not the causative agent in AAA pathogenesis in this patient. The rapidly progressive anemia may result from the increased destruction of red blood cells as evidenced by the presence of anisocytosis, acanthocytes, and schistocytes in mature erythrocytes, and the decreased platelet count may be caused by the increased consumption of platelet as evidenced by the platelet transfusion refractoriness.

Dimethylbenzene is a well-known genotoxic agent. In addition to AAA, the genotoxicity of dimethylbenzene exposure has been recognized to be closely linked to the pathogenesis of MDS and acute leukemia as well^[1,39]. In the present case, dimethylbenzene is the only noticeable history of genotoxic exposure. Although clonal evolution frequently develops due to the selective pressure in the context of severe immunological attack and gradual loss of HSPCs, and may be responsible for the progression and exacerbation of impaired hematopoietic capacity as evidenced by the

gradual loss of sensitivity to CsA treatment, it is unconceivable that the gene damages caused by these spontaneous mutations were accumulated so enriched that they are sufficient to induce malignant transformation within only 4 mo, meaning that the oncogenic genes had pre-existed, most probably initiated by the genotoxicity of dimethylbenzene exposure preceding the onset of AAA and precipitated by subsequently spontaneous mutations and selective pressure. Furthermore, the 23-year history of hypocellular and fat-replaced BM, several recurrences in the intermittence of GCP treatments (indicating the resilience of BMS), and the emergence of MCH that occurred only after the successive administration of rifampicin and berberine with monthly administered GCP, also suggest that the immunogenic antigens on HSPCs had pre-existed for a very long time. Xin *et al.*^[40] established an animal model of AAA by using Mx1Cre⁺TGF β -activated kinase-1(Tak1)^{fx/fx} (Tak1^{mut}) mice in which the gene encoding *Tak1* could be spontaneously mutated in a small subset of hematopoietic cells and the suppressive effect on proliferation and differentiation merely occurred in mutated cells. In this animal model, high levels of IFN- γ and TNF- α were identified, and the characteristic AAA morphology developed with a necroptotic manner of cell death, suggesting that BMS could be caused by the bystander insult that was originated from the genetically damaged hematopoietic cells. Despite the absence of direct evidence in the present case due to the lack of more complex and elegant laboratory investigations, the emergence of MCH following the settlement of myelosuppression raises the intriguing possibility that immunogenic neo-epitopes on genetically damaged hematopoietic cells caused by either genotoxic agents or by spontaneously mutated genes may become the directly targeted antigens of host's potential immunological surveillance against malignant cells and may thereby induce a proinflammatory niche in the BM^[14-18,21-23], one of the consequences of which results in severe hypoplastic BM *via* the chronic overproduction of proinflammatory mediators superimposed upon non-targeted neighbouring inculcable cells^[4-6,40] but yet probably without clear evidence of dysmorphic features. The undetected MCH when he was first referred to our center 7 year earlier may be attributable to the extraordinarily reduced number of hematopoietic cells due to the paucicellular and fat-replaced BM, especially the stealth malignant cells due to the host's potential immune surveillance that was beyond the capacity of being identified by the conventional laboratory tests. Although clonal evolution could not be completely excluded, it is tempting to speculate that the emergence of MCH is most likely due to the relief of BMS by the synergistic effects of successful treatment of GIC together with the immunosuppressive therapy. When BMS had been relieved, MCH became evident. From this point of view, commensal microbiome in GIC is unlikely to be the original trigger but rather an intensifier *via* the adjuvant effect by innate immune cells sensing commensal microbes and their metabolites on the background of the presence of antigenic products on targeted cells as the initiating factor and the pre-existence of abnormally activated CTLs in genetically susceptible subjects. If this is true, it could be inferred that the specific immune responses to targeted antigens on HSPCs alone were not sufficient to sustain the chronic inflammatory niche in the BM. It is the chronic inflammatory state generated in response to the constant exposure of host immune cells to the intestinally derived antigens due to the increased permeation of impaired intestinal barrier is critically required for the emergence, development, and progression of AAA. This combined effect of specific immune responses to HSPCs with intestinally derived stimulation appears to be much easier to interpret the preferential insult to HSPCs and the critical requirement of chronic inflammatory conditions. In a similar way, the bystander effect may also play an important role in AAA patients whose pathogenesis is associated with infectious agents (viruses, bacteria, spirochetes, helminths, and so on) that are able to chronically infect and proliferate in hematopoietic cells, immune cells, or the BM environment^[41-45].

As discussed above, it could be extrapolated that, at least in a subgroup of AAA patients, the constant expression of immunogenic neoplastic products on hematopoietic precursors is the initiating factor of such autoimmune responses, and the functional inhibition of normal hematopoiesis may be the consequence of bystander insult that arises from the immune surveillance against malignant cells, in the pathogenic process of which overproduced proinflammatory mediators play a direct inhibitory and pro-apoptotic role. The impaired structural and functional integrity of intestinal barrier may reinforce the myelosuppressive process by offering an adjuvant effect to augment the intensity of systemic inflammatory state and maintain the high sensitivity of autoreactive CTLs. This cellular immune-mediated mechanism characterized by IFN- γ -predominated functional inhibition, commonly in a way of apoptosis or necroptosis, of autologous hematopoiesis, also probably playing a fundamental role in the pathogenesis of hMDS and a subgroup of low risk MDS, is

completely distinct from the pathogenic mechanisms in classic MDS that is characterized by the hypercellular BM and ineffective hematopoiesis, in which the innate immune responses were directly elicited by pattern recognition receptors sensing damage-associated molecular patterns in the genetically damaged hematopoietic precursors with the features of increased proliferative activity of clonal hematopoiesis, inflammasome formation, cell death in a manner of pyroptosis, TNF- α predominance, and effective lenalidomide treatment^[46-48]. The significance of identification of the initiating factors and recognition of the pathogenic mechanism lies in that it would be helpful for doctors to select an optimal therapeutic approach and to improve the treatment outcome, not only targeting immune-mediated mechanisms as the generally accepted first-line ISTs but also taking into account the initiating factors and the sustaining forces. Overall, the extrapolation is only an indirect implication from the treatment process of a RSAA patient, and further investigations are critically needed to look for the direct evidence and to illustrate the precise mechanism.

ACKNOWLEDGEMENTS

The authors would like to thank Zhe Yong (Department of Blood Pathology, The Affiliated Hospital of Qingdao University) for assistance in the validation of morphological diagnosis, and Xiu-Shuan Feng (Department of Radiology, The Central Hospital of Qingdao West Coast New Area) for assistance in the reassessment of computerized tomography images.

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