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Flared inflammatory episode transforms advanced myelodysplastic syndrome into aplastic pancytopenia: A case report and literature review

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

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Abstract

BACKGROUND

Myelodysplastic syndrome (MDS) is a hematological neoplasm, and an increase in myeloblasts is representative of leukemic hematopoiesis in advanced MDS. Low-risk MDS usually exhibits deranged autoimmunity resembling that of aplastic anemia (AA), whereas advanced MDS is characterized by a phenotype of immune exhaustion. MDS can be normo/hyperplastic or hypoplastic. Generally, bone marrow cellularity and myeloblasts increase with disease progression. Transformation from advanced MDS to AA-like syndrome with leukemic cell regression has not previously been reported.

CASE SUMMARY

A middle-aged Chinese woman had a 4-year history of leukocytopenia. Six months prior to admission, the patient developed gradually worsening fatigue and performance status. The leukocytopenia further progressed. She was diagnosed with MDS with excess blasts-2 based on increased bone marrow cellularity and an increased percentage of myeloblasts on marrow and blood smears, an increased percentage of cluster of differentiation (CD)34+CD33+ progenitors in immunotyping analysis, a normal karyotype in cytogenetic analysis, and the identification of somatic mutations in *CBL*, *KMT2D* and *NF1* in molecular analysis. Initially, neutropenia was the predominant hematological abnormality, with mild anemia and thrombocytosis, and the degree of fatigue was far more severe than the degree of anemia. In the following months, the patient experienced several febrile episodes. Intravenous antibiotic treatments were able to control the febrile episodes, but the elevated inflammatory indices persisted. The hematological parameters dramatically fluctuated with the waxing and waning of the inflammatory episodes. With recurrent flares of the inflammatory condition, agranulocytosis and severe anemia developed, with mild thrombocyt-

openia. During the patient's hospitalization, computed tomography (CT) scans revealed the presence of extensive inflammatory lesions involving the lungs, mediastinum, pleura, gastrointestinal tract, peritoneum and urinary tract, with imaging features suggestive of the reactivation of disseminated tuberculosis. Reevaluation of the bone marrow smears revealed that the cellularity became hypoplastic, and the leukemic cells regressed, suggesting that both normal and leukemic hematopoiesis had been heavily suppressed. Immunological analysis of the bone marrow samples revealed a decreased percentage of CD34+ cells and an immunological signature resembling that of severe AA (SAA), confirming the regression of the leukemic cells by autoimmune-mediated attacks. The patient demonstrated resistance to multiple drugs, including antituberculotics, recombinant human granulocyte colony-stimulating factor, broad-spectrum antibiotics, voriconazole, ganciclovir, immune suppressants, eltrombopag and intravenous immunoglobulin, which further worsened the hematological injury and patient's performance status. The patient eventually died of overwhelming infection and multidrug resistance.

CONCLUSION

Advanced MDS can transform to aplastic cytopenia with leukemic cell regression and an immunological signature of SAA during inflammatory flare-ups.

Key Words: Myelodysplastic syndrome; Aplastic anemia; Inflammatory stress; Leukemic cell regression; Antileukemic; Case report

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Core Tip: In patients with myelodysplastic syndrome, bone marrow cellularity and the percentage of myeloblasts generally increase with disease progression. Transformation from advanced myelodysplastic syndrome to aplastic cytopenia with leukemic cell regression has not previously been reported. Here, we report a case of this disease phenotypic transformation. The cause for the disease transformation was a disseminated inflammatory condition involving the lungs, mediastinum, pleura, gastrointestinal tract, peritoneum and urinary tract. This case study demonstrated that in myeloid neoplasms, disseminated inflammatory conditions can suppress both normal and leukemic hematopoiesis.

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INTRODUCTION

Myelodysplastic syndrome (MDS) is a hematological clonal disease caused by somatic mutations in myeloid neoplasm-associated genes, resulting in malignant proliferation and ineffective hematopoiesis. Clinically, impaired blood cell production leads to peripheral cytopenia and resultant symptoms. Morphologically, MDS is characterized by one or more lineages of marrow dysplasia, and an increased percentage of myeloblasts and cluster of differentiation (CD)34+ cells is representative of leukemic hematopoiesis and the most significant dysplastic feature in the diagnosis and risk stratification. The identification of somatic mutations in myeloid neoplasm-associated genes is helpful in determining malignant hematopoiesis[1-3]. Aplastic anemia (AA) is a disease of hematopoietic failure caused by cellular immune-mediated destructive impairment of hematopoietic progenitor cells. Decreased hematopoietic volume and deranged autoimmunity are the underlying pathophysiology in AA development and diagnosis[4-6]. AA is generally considered a benign hematological disorder. By definition, AA and MDS are distinctive disease entities. However, studies using modern techniques have demonstrated that AA and MDS exhibit overlapping signatures and an intrinsic relationship with respect to laboratory abnormalities and prognostic outcomes[7]. Patients with definitively diagnosed AA may have somatic mutations typically seen in MDS[8,9], and patients with low-risk MDS, particularly hypoplastic MDS, exhibit an immunological signature typically seen in AA[10-11], indicating that immune function may impact the disease phenotype.

MDS can be normo/hyperplastic or hypoplastic, and the bone marrow cellularity and percentage of leukemic cells generally increases with disease progression. The increased leukemic cells are usually ascribed to leukemic cell expansion *via* the acquisition of proliferative advantage or escape from

immune-mediated attacks[8,9,12,13]. Although disease phenotypic transformation from severe AA (SAA) to myeloid neoplasms following antithymocyte globulin (ATG) and cyclosporine-based immunosuppressive therapy (IST) is well recognized, phenotypic transformation from advanced MDS to aplastic cytopenia with regression of leukemic cells has not been reported. In this manuscript, we report a patient with definitively diagnosed MDS with excess blasts-2 (MDS-EB-2) who exhibited disease phenotypic transformation from advanced MDS into aplastic cytopenia with the development of deranged cellular immune-mediated responses and concomitant leukemic cell regression. Due to the slowly progressive infectious disorder, we were able to document the transformation process. Initially, the patient presented with neutropenia, mild anemia and thrombocytosis. During the following 6 mo, the patient experienced several febrile episodes; intravenous administration of antibiotics was able to control the febrile episodes, but the elevated inflammatory indices persisted. The hematological parameters fluctuated with the waxing and waning of the inflammatory condition. With recurrent flares of the inflammatory condition, aplastic pancytopenia developed, with cytological and immunological features resembling those of SAA. Computed tomography (CT) scans revealed extensive inflammatory lesions involving the lungs, mediastinum, pleura, gastrointestinal tract, peritoneum and urinary tract, with imaging features suggestive of the reactivation of disseminated tuberculosis. However, the patient exhibited multidrug resistance, which further worsened the hematological injury and patient's performance status.

CASE PRESENTATION

Chief complaints

Worsening fatigue and progressive cytopenia for 6 mo.

History of present illness

Six months prior to admission to our hospital, a 46-year-old Chinese woman sought medical help at another hospital due to gradually worsening fatigue and leukocytopenia. The patient was diagnosed with MDS-EB-2 based on increased bone marrow cellularity and an increased percentage of myeloblasts (representing 13% of the total nucleated cells) on morphological evaluation of bone marrow smears (Figure 1A) and slices (Figure 1B). The diagnosis was further supported by an increased percentage of CD34+CD33+ hematopoietic progenitors (7.18%) on immunological analysis, a normal 46;XX karyotype on cytogenetic analysis, and the identification of somatic mutations in *CBL* [a variant allele fraction (VAF) of 3.5%], *KMT2D* (a VAF of 40.1%) and *NF1* (a VAF of 44.5%) on molecular biological analysis. At the time of diagnosis, complete blood count (CBC) revealed the following results: white blood cells (WBCs), $1.74 \times 10^9/L$; absolute neutrophil count, $0.38 \times 10^9/L$; red blood cells (RBCs), $3.02 \times 10^{12}/L$; hemoglobin level (Hb), 102 g/L; platelets (Plts), $356 \times 10^9/L$; and absolute reticulocyte count (Ret), $64.26 \times 10^9/L$. Neutropenia was the predominant hematological abnormality, with mild anemia and thrombocytosis. The degree of fatigue was far more severe than the degree of anemia. The patient was treated with Chinese herbs, which failed to achieve any hematological improvement and resulted in worsening cytopenia. During the following 6 mo, the patient experienced several febrile episodes. Intravenous antibiotics were able to control the febrile episodes, but the elevated inflammatory indices persisted, and the inflammatory disease lacked localized signs and symptoms. Various imaging modalities and laboratory tests failed to determine the location or etiology of the inflammatory condition. During the inflammatory episodes, neutropenia worsened, frequently accompanied by a dramatic reduction in platelet count. After the febrile episodes were controlled, the hematological parameters were significantly improved. With recurrent flares of the inflammatory condition, thrombocytopenia and severe anemia emerged, and neutropenia further worsened. Four hours prior to admission, a febrile episode recurred, with the highest body temperature being 39.2 °C. During this febrile episode, the patient was transferred to our hospital.

History of past illness

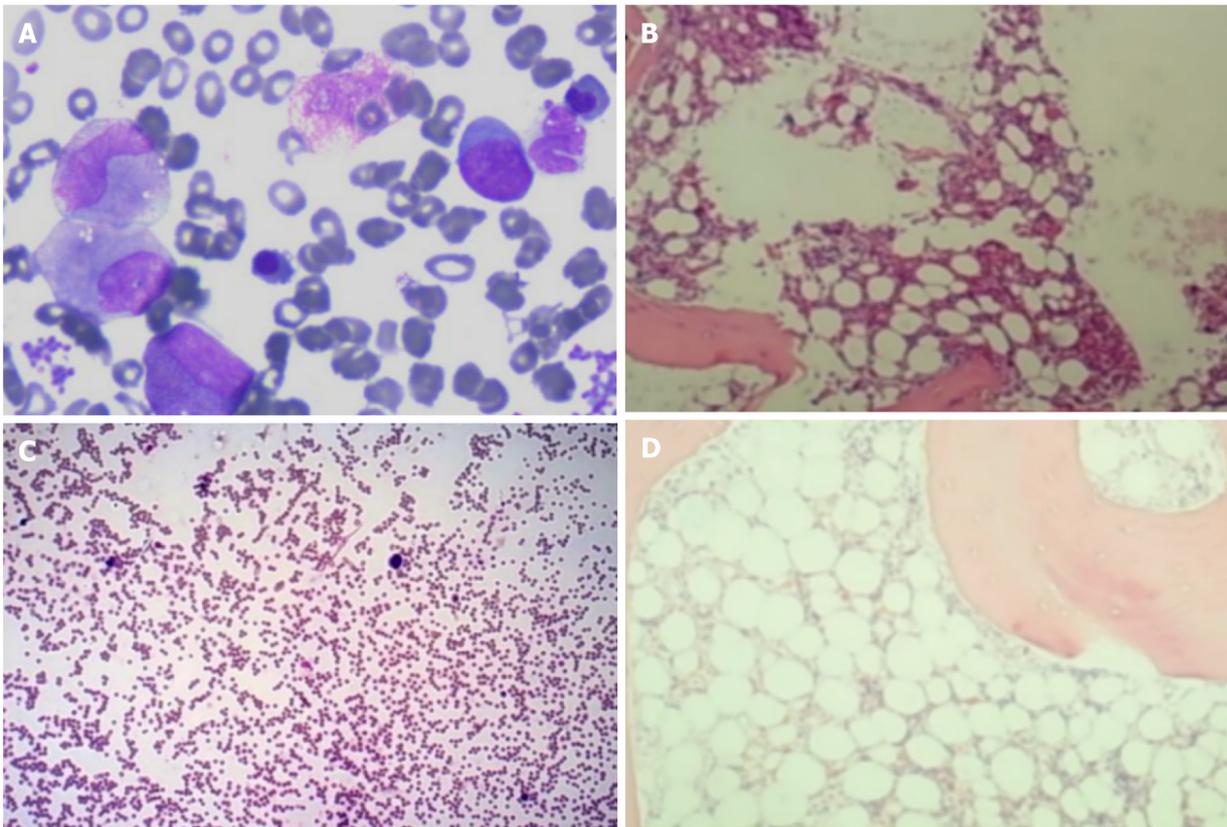
The patient had a 4-year history of leukocytopenia, which was found during physical check-ups. She denied any history of cardiovascular, endocrine, respiratory, gastrointestinal, urogenital or musculoskeletal diseases.

Personal and family history

No family history of inherited, hematological, autoimmune or neoplastic diseases was recorded.

Physical examination

The patient was 154 cm tall and weighed 42.5 kg. Upon admission, her vitals were as follows: Temperature 39.0 °C, respiratory rate 19 breaths per minute, heart rate 80 beats per minute, and blood pressure 133/78 mmHg. Physical examination revealed mild tenderness of the right iliac fossa. No significant abnormalities of the nervous, respiratory, cardiovascular, or musculoskeletal systems were



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Figure 1 Morphological and pathological evaluation of the bone marrow at the time of initial diagnosis of myelodysplastic syndrome and in the flared inflammatory episode. A and B: Morphological (A) and pathological (B) evaluation of the bone marrow at the time of initial diagnosis of myelodysplastic syndrome showed significantly increased cellularity with an increased percentage of myeloblasts that accounted for 13% of the total nucleated cells; C and D: Morphological (C) and pathological (D) reevaluation of the bone marrow in the flared inflammatory episode with agranulocytosis and severe anemia showed heavily decreased cellularity with regression of the leukemic cells.

found.

Laboratory examinations

Routine laboratory examinations: At the emergency department, CBC revealed the following: WBCs, $0.47 \times 10^9/L$; ANC, $0.17 \times 10^9/L$; RBC, $1.07 \times 10^{12}/L$; Hb, 59 g/L; Plts, $94 \times 10^9/L$; Ret, $12.2 \times 10^9/L$; and C-reactive protein (CRP), 59.27 mg/L. The coagulation profile demonstrated an elevated plasma fibrinogen level (4.41 g/L), with a D-dimer of 0.92 mg/L. Urinalysis revealed an occult blood of 2+, protein of 1+, RBC of 186/ μ L and WBC of 45/ μ L. Feces examination revealed a mucopurulent bloody stool, with an occult blood of 3+, and With the exception of a slightly decreased serum albumin level and slightly increased serum levels of lactate dehydrogenase, hydroxybutyric dehydrogenase, and β 2-microglobulin, no other obvious abnormalities were detected on biochemical tests. The immunological tests for hepatitis A, B, and C virus and human immunodeficiency virus were negative. Repeated blood cultures were negative for growth of both Gram-positive and Gram-negative microbes. Antinuclear antibodies and neoplastic biomarkers were also negative, but an antineutrophil cytoplasmic antibody was positive. A positive interferon-gamma (IFN- γ) release assay raised the suspicion of tuberculosis infection. However, acid-fast bacilli could not be identified upon repeated sputum examinations.

Specific laboratory examinations for blood diseases: After hospitalization, the patient's neutropenia and anemia worsened further, and there was significant progression of thrombocytopenia. Coomb' test reported a negative result, which ruled out the peripheral antibody-mediated pathogenic process. Reevaluation of the bone marrow samples was performed. Cytological evaluation of the bone marrow smears (Figure 1C), and slices (Figure 1D) indicated that the cellularity became heavily hypoplastic and the hematopoietic volume was significantly reduced, with an increased percentage of various stages of nucleated erythrocytes (61%) and the absence of morphological dysplasia. Myeloblasts were rarely visualized, indicative of regression of the leukemic clones. Megakaryocytes were also rarely visualized, confirming the decreased platelet production. Immunological analysis revealed significantly decreased percentages of CD34+ cells (0.51%), CD19+ cells (5.43%), and CD4+ cells (7.01%) and significantly increased percentages of CD71+ cells (43.73%), CD8+ cells (18.25%), and CD5+CD7+ cells (7.64%), an immunological signature consistent with autoimmune hematopoietic failure. The elevated serum levels

of interkin (IL)-6, IFN- γ and tumor necrosis factor (TNF)- α also suggested the development of dysregulated cellular immune responses. CD55 and CD59 expression was within the normal levels (97.25% and 96.63 on erythrocytes and 99.42% and 98.06% on granulocytes). Cytogenetic analysis revealed a normal 46,XX karyotype. Molecular analysis revealed the presence of somatic mutations in *CBL* (2.8%), *KMT2D* (37.6%) and *NF1* (44.6%), consistent with the mutations detected when the patient was initially diagnosed with MDS-EB-2, but the VAFs were slightly decreased. These morphological, immunological, and cytogenetic analyses favored a diagnosis of SAA[4-6], but the presence of myeloid neoplasm-associated somatic mutations and the medical history suggested a diagnosis of hMDS[1,2,9,10].

Imaging examinations

Chest (Figure 2) and abdominal (Figure 3) CT scans revealed the presence of extensive inflammatory lesions involving the lungs, mediastinum, pleura, gastrointestinal tract, peritoneum and urinary tract. The imaging features were suggestive of the reactivation of disseminated tuberculosis[14,15]. Endoscopic examination revealed the presence of successional inflammatory lesions extending from the terminal ileum to the sigmoid colon and a mixture of old and novel cicatricial tissues in the terminal ileum and cecum. The pathological examination reported mucositis. The inflammatory nature of the ileocecal lesions was corroborated using positron emission tomography (PET)/CT.

FINAL DIAGNOSIS

The patient was diagnosed with hMDS with suspected tuberculosis reactivation.

TREATMENT

In the following 6 mo of hospitalization, the patient was treated with the standard first-line antituberculars (consisting of rifampicin, isoniazid, ethambutol and pyrazinamide) for suspected tuberculosis infection, recombinant human granulocyte colony-stimulating factor (rhG-CSF) for agranulocytosis, sequential administration of intravenous antibiotics (piperacillin-tazobactam, kanamycin, levofloxacin, vancomycin, voriconazole) for suspected bacterial infections due to agranulocytosis, ganciclovir for possible herpesvirus infections (because herpesvirus infections have been reported to be common microbes in the pathogenesis of immune-mediated hematopoietic failure), glucocorticoids and cyclosporine for immune-mediated pathophysiology, eltrombopag to promote autologous hematopoiesis, intravenous immunoglobulin for possible parvovirus B19 infection (because parvovirus B19 infection has been reported to be a common microbe in the pathogenesis of immune-mediated hematopoietic failure), and polyethylene glycol and electrolyte oral solution (a gut-cleansing preparation) to rapidly remove pathogenic bacteria and their endotoxins in the intestinal lumen.

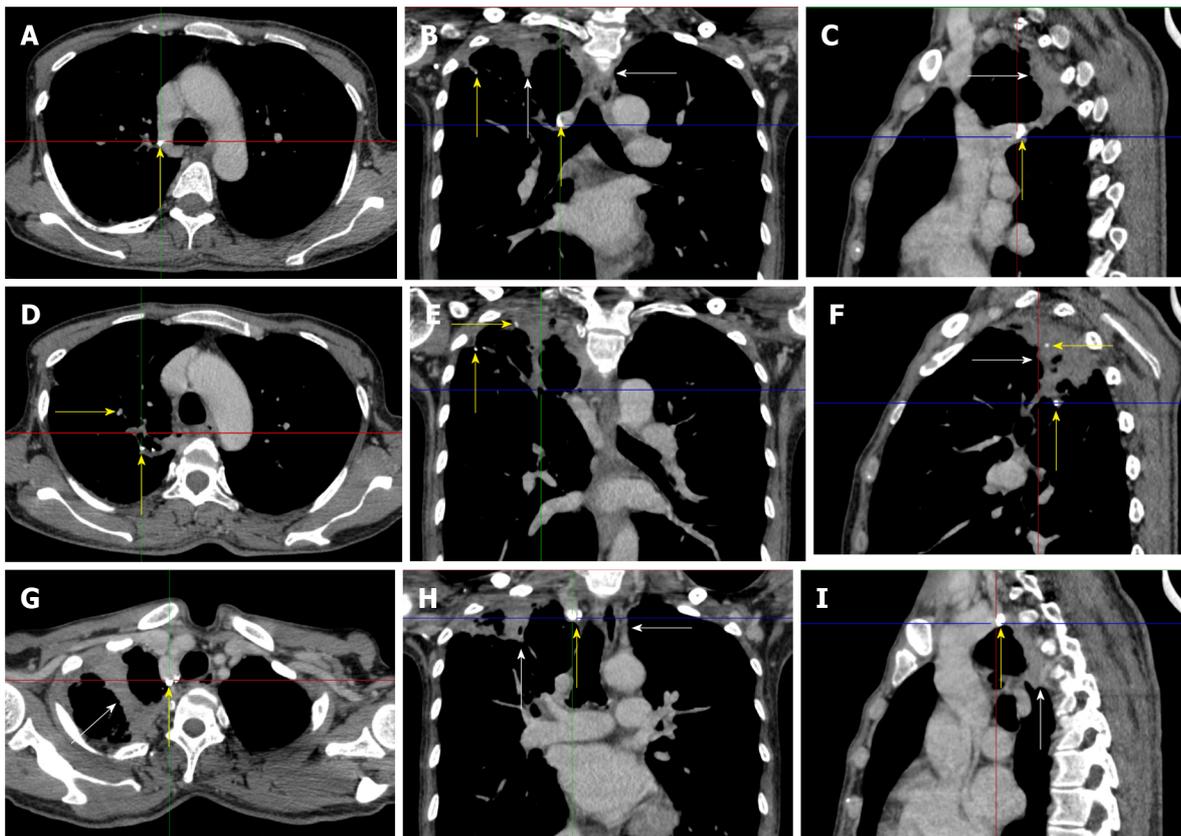
OUTCOME AND FOLLOW-UP

The patient demonstrated resistance to these treatment modalities, and multidrug resistance resulted in the aggravation of the systemic and gut inflammatory condition, indicating that the gut inflammatory disease was likely complicated by other unknown and intractable causative agents. The patient's hematopoietic injury and performance status further deteriorated, and she developed severe aplastic pancytopenia, cachexia, and platelet transfusion refractoriness. Because of the poor performance status and platelet transfusion refractoriness, surgical interventions were denied. The patient eventually died of systemic inflammatory response syndrome and cachexia.

DISCUSSION

In this case study, we described a patient with definitively diagnosed MDS-EB-2 who, following repeated flares of a disseminated inflammatory disease, developed severe aplastic cytopenia, with regression of the leukemic cells.

The definitive diagnosis of MDS-EB-2 was made at another hospital based primarily on the increased percentage of myeloblasts and CD34+ hematopoietic progenitors and the identification of myeloid neoplasm-associated somatic mutations in bone marrow samples, which are the most reliable markers for leukemic hematopoiesis and the most valuable parameters in MDS diagnosis and risk stratification [1,2,11]. Initially, neutropenia was the predominant hematological abnormality, with concurrent mild anemia and thrombocytosis. The degree of fatigue was far more severe than the degree of anemia, strongly indicative of an active inflammatory condition leading to systemic inflammatory symptoms. In



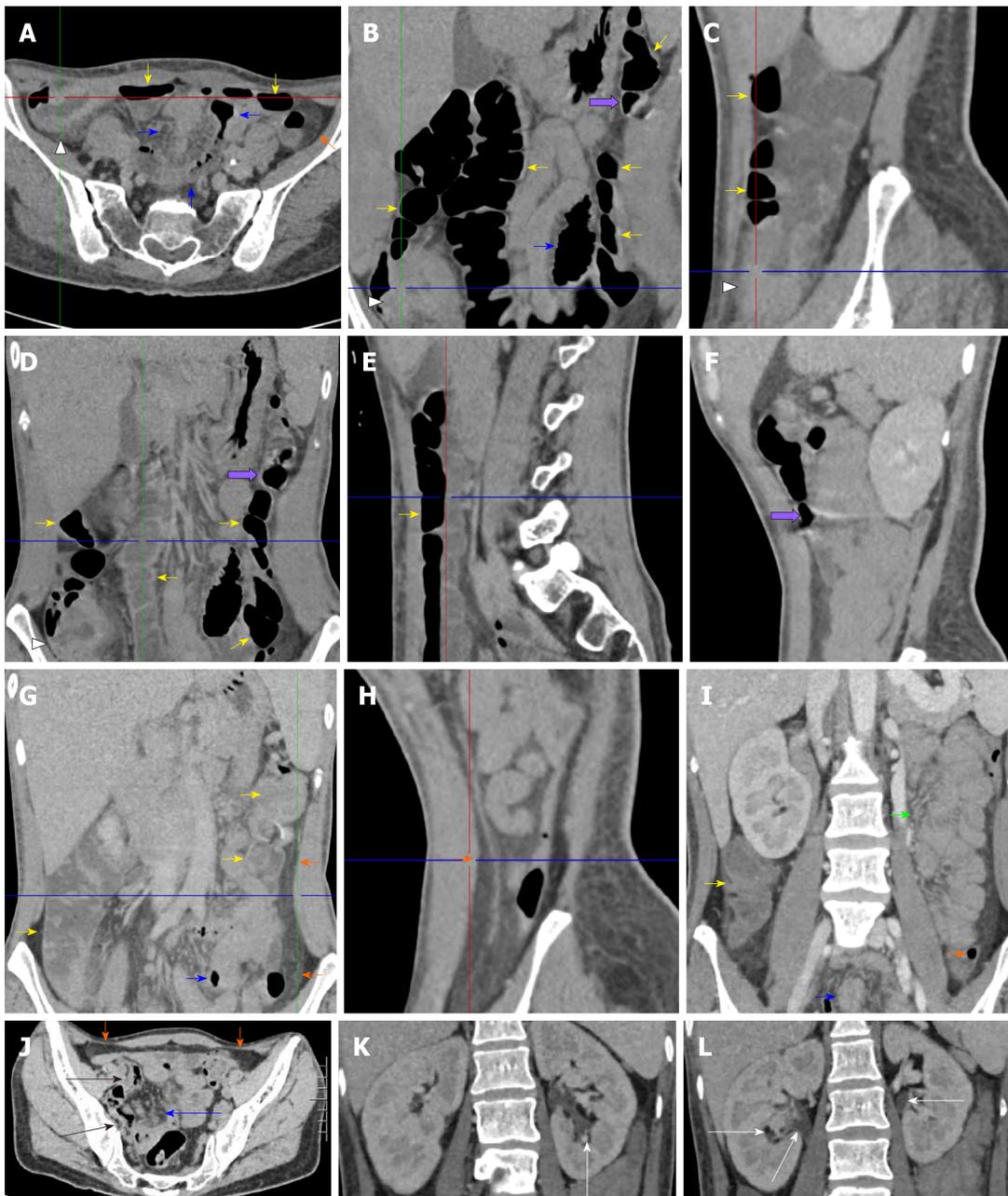
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Figure 2 Chest computed tomography scan in the flared inflammatory episode. Multiple calcified lesions (yellow arrows) with adjacent exudative lesions (white arrows) were present in the right upper lung and mediastinal lymph nodes, indicating the presence of old tuberculosis infection. A-C: A large calcified lesion was present in the posterior mediastinum with adjacent exudative lesions; D-F: Successional exudative lesions on a background of calcified lesions formed a large fused exudative lesion present in the right upper lung abutting the pleura and mediastinum; G-I: A large calcified lesion was present in the top of the right upper lung with adjacent exudative lesions. This imaging feature is typical of the reactivation of an old tuberculosis infection.

the following months, the inflammatory response worsened, her performance status deteriorated, and aplastic cytopenia developed. She experienced several febrile episodes. During the febrile episodes, neutropenia worsened, uniformly accompanied by a significant decrease in the platelet count. Upon resolution of each febrile episode, the hematopoietic parameters were significantly improved, strongly suggesting that the aggravated inflammatory reaction dramatically affected hematological function. Although intravenously administered antibiotics were able to control the febrile episodes, the elevated inflammatory indices persisted, indicating the presence of an active chronic inflammatory disease. The inflammatory disease and underlying etiology were not definitively diagnosed and effectively managed, resulting in persistent neutropenia. When sent to our hospital, the patient presented with a febrile episode. Pancytopenia emerged with agranulocytosis and severe anemia, but thrombocytopenia was mild. CT scans revealed the presence of extensive inflammatory lesions involving the lungs, mediastinum, pleura, gastrointestinal tract, peritoneum and urinary tract, with imaging features suggestive of the reactivation of disseminated tuberculosis. The IFN- γ release assay and endoscopic examination also supported the diagnosis of tuberculosis infection. The inflammatory nature of the ileocecal lesions was corroborated using PET/CT. However, the patient failed to respond to treatments with rhG-CSF, antitubercotics, broad-spectrum antibiotics, voriconazole, ganciclovir, intravenous immunoglobulin and gut-cleansing preparation (GCP).

After admission, the hematological profile rapidly deteriorated, and the patient developed severe pancytopenia. Reevaluation of the bone marrow smears was performed. Cytological evaluation demonstrated that the cellularity had become hypoplastic, and previously increased myeloblasts was no longer evident. Immunological analysis confirmed the decreased percentage of myeloblasts and cellular immune-mediated autoimmunity. These cytological and immunological features were similar to those of SAA. Based on the disease progression, it could be interpreted that the recurrent febrile episodes and the aggravated systemic inflammatory response were responsible for suppression of both normal and leukemic hematopoiesis, resulting in the disease phenotypic transformation from advanced MDS to SAA feature.

This case study revealed the following attractive points:



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Figure 3 Enhanced abdominal computed tomography in the flared inflammatory episode. The computed tomography (CT) scan was performed after bowel preparation. A-C: Striking bowel wall thickening with mucosal hyperenhancement, mucosal hyperdensity and circumferentially distributed hypervascular fat stranding of the cecum in the right iliac fossa in the absence of mural stratification was readily visualized (head arrows). From the ascending colon to the splenic flexure, the mucosa was hyperenhanced and hyperdense, and the lumen was dilated with successional gas-liquid levels (yellow arrows), suggesting the fibrotic thickening of the colonic wall and the presence of dynamic abnormalities. Noticeably, the location of the transverse colon was abnormally low, which may represent a visceral ectopia and may affect colonic function. However, the descending colon was collapsed following a segment of hypertrophic lesions in the splenic flexure, and in some segments, was emptied. In a short segment of the sigmoid colon (blue arrows), the mucosa was hypertrophic, and the lumen was dilated. Proximal and distal to the dilated segment of the sigmoid colon, the colonic wall was hypertrophic, and the lumen was collapsed; D and E: Successional gas-liquid levels in the descending part of the transverse colon; F: A segment of hyperenhanced mucosa and hypertrophic wall with erosive lesions was present in the ascending part of the transverse colon (purple arrows). These hypertrophic lesions could also be seen in multiple colonic and enteric segments; G and H: A misty fat streak on both the visceral and parietal sides of the thickened peritoneum of the left abdominal wall (orange arrows) was visualized along the ascending part of the transverse colon, indicating the peritoneal involvement of inflammatory lesions. An inflamed diverticulum was present in the distal descending colon, and the fat streak was especially prominent adjacent to this colonic segment; I: A large segment of clustered and adhered bowel loop was present in the jejunum (green arrow), together with fibrotic thickening of the peritoneum forming a so-called "abdominal cocoon". Clustered perienteric hypervascular fat stranding was adjacent to this adhesive jejunal loop. This clustered perienteric hypervascular fat stranding could also be visualized in other enteric segments (blue arrows); J: The fat streak was contiguous with the fat stranding of the right iliac fossa posterior to the anterior abdominal wall at the pelvic level (orange arrows). The wall of the distal ileum was hypertrophic, and the lumen was gas-filled (black arrows); K and L: Hydronephrosis was present in the bilateral pelvises (white arrows), and hypertrophic lesions could be visualized. These imaging features, together with the imaging presentation on chest CT, strongly suggested a diagnosis of tuberculosis reactivation involving the gastrointestinal tract, peritoneum and pelvises.

First, a severe inflammatory condition can heavily suppress hematopoietic function and reduce bone marrow cellularity in predisposed individuals, resulting in the development of autoimmune hematopoietic failure - whether it was called SAA or hMDS. It is not surprising in light of hematopoietic regulation mechanisms. Blood cells themselves are immune cells and are generated from the division and maturation of hematopoietic stem cells. Their production is regulated largely in response to pathogenic invasion and antigen stimulation. When confronting an acute and limited microbial infection, blood cell production switches the differentiation to replenish effector immune cells to fight the ongoing infection at the expense of self-renewal capacity of hematopoietic progenitors[16,17]. After pathogenic antigens are cleared, the activated host immune system quickly returns to the homeostatic state, and blood cell production quickly returns to steady-state hematopoiesis. However, persistent and intensive antigen stimulation can perturb the immune regulatory mechanisms, thereby generating a large number of persistently activated immune cells and secreting a large amount of inflammatory mediators. Activated cytotoxic T lymphocytes (CTLs) and increased levels of inflammatory mediators result in the suppression of autologous hematopoiesis and the exhaustion of hematopoietic progenitors [18,19], especially in the setting of genetically damaged hematopoietic progenitors and a neoplastic molecule-initiated marrow immune-active environment[20-22]. In neoplastic molecule-initiated bone marrow immune-active environment, the overexpressed human leukocyte antigen-DR (HLA-DR), Toll-like receptors (TLRs) and Fas molecules on hematopoietic progenitors enhance the immunological responses to exogenous antigen stimulation[20-24]. However, the phenomenon observed in this case study has not previously been reported, because in most cases, the development of severe aplastic cytopenia in end-stage myeloid neoplasms progresses very quickly, and patients rapidly die of overwhelming infections and cytokine cascades. Another reason is likely because bone marrow reevaluations are seldom performed in these definitively diagnosed MDS patients.

Second, leukemic cells can regress during inflammatory flare-ups, suggesting that autoimmune-mediated hematopoietic failure likely functions as an inflammatory stress-fueled antileukemic mechanism. With recurrence of the febrile episodes and aggravation of the inflammatory condition, together with reduced bone marrow cellularity, the morphologically evidenced leukemic clones disappeared. Leukemic cell regression suggests the preferential suppression of malignant proliferation and represents an inflammatory stress-fueled antileukemic activity. In this stage, a deranged autoimmune signature resembling that seen in patients with SAA was observed[10-12]. AA is generally considered a benign hematological disorder[4,5], whereas MDS is an unequivocal hematological neoplasm, especially when presenting with an increased percentage of myeloblasts[1-3]. However, with the widespread application of next-generation sequencing techniques in the diagnosis and risk stratification of hematological diseases, patients with definitively diagnosed AA have been found to have somatic mutations that play well-known roles in neoplastic pathogenesis. Approximately 15% of AA patients have neoplastic cytogenetic abnormalities, and approximately 30% of AA patients have myeloid neoplasm-associated somatic mutations[8,9]. The percentage of somatic mutations increases up to 60% after ATG and cyclosporine-based IST, along with an increase in the leukemic burden[25]. Approximately 10%-15% of AA patients undergo leukemic transformation after ATG and cyclosporine-based IST, some of whom progress to myeloid neoplasms during IST or within 6 mo following IST[25-27], strongly suggesting that the leukemic clones preexisted but were concealed in the AA stage and rapidly expanded following IST. Furthermore, AA and low-risk MDS, especially hypoplastic MDS, share similar immunological features, that is, cellular immune-mediated responses[10-12]. AA and low-risk MDS also share similar prognostic outcomes. Together, this evidence suggests that AA and MDS likely have an intrinsic relationship with respect to their pathogenesis and immunological signature. In organ-specific autoimmune diseases, the primary immune-active bone marrow environment is induced by CTL recognition of neoplastic antigens or by innate immune cell recognition of damage-associated molecules on hematopoietic progenitors, whereas active chronic inflammatory conditions fuel antileukemic activities[28,29] in the setting of overexpression of HLA-DR, TLRs and Fas molecules on damaged hematopoietic progenitors[20,21,24]. With successful treatment of the inflammatory condition, the leukemic clone undergoes expansion, and morphologically evidenced myeloid neoplasms emerge. The same effect can also be achieved by ATG-based IST. When the inflammatory conditions are aggravated, the leukemic clones are concealed, and the morphologically evidenced myeloid neoplasms disappeared.

Third, neutropenia can be the primary hematological abnormality in immune-mediated hematopoietic failure and myeloid neoplasms under active chronic inflammatory conditions. The patient in our case study had a 4-year history of leukocytopenia before she was diagnosed with MDS-EB-2. With aggravation of the inflammatory condition, a decrease in granulocytes was the earliest and most prominent hematological abnormality, with poor sensitivity to rhG-SCF, which was also indicative of the preferential suppressive activity on myelopoiesis and autoimmune responses to myeloid progenitors. Autoimmune neutropenia can be preexisting for many years before the development of a morphologically evidenced myeloid neoplasm, and in this stage, the leukemic clones are concealed. The bone marrow may exhibit hypocellularity, with cytological and immunological features resembling those of immune-mediated hematopoietic failure[30,31]. Poor response to rhG-SCF treatment predicts an increased risk for transformation to myeloid neoplasms[31]. In fact, a significant proportion of patients with myeloid neoplasms present with neutropenia upon initial diagnosis or during disease

progression, and these patients frequently exhibit longer survival.

Finally, gastrointestinal involvement of inflammatory conditions may play a more important role in the repression of hematopoietic function. In this patient, the imaging features of the chest CT scan were typical for the reactivation of pulmonary tuberculosis[32,33], and the imaging features of the abdominal CT scans suggested a diagnosis of gastrointestinal tuberculosis with peritoneal involvement[14,15]. Although immune-mediated hematopoietic failure has been reported to be associated with tuberculosis [34-38] and Bacillus Calmette-Guerin (BCG) vaccination[39], the tuberculosis infection was disseminated rather than isolated pulmonary tuberculosis. Effective suppression of marrow hematopoiesis requires the engagement of sufficient activated immune cells and a large amount of proinflammatory cytokines. The gastrointestinal tract contains a large number of lymphatic tissues and a complex microbial community and therefore can provide sufficient activated immune cells and continuously supply intestine-derived pathogenic antigens[40,41]. Not only pathogenic microbes but also commensal microbes and undigested food can become exogenous antigens to activate CTLs and stimulate the release of proinflammatory cytokines[42-44]. Gut dysbiosis and inflammatory bowel diseases have been reported to be associated with immune-mediated hematopoietic failure[45-48]. A gluten-free diet[46], resection of diseased intestinal segments[47] or successful treatment of inflammatory bowel diseases[48] can achieve hematological remission, confirming the role of dysbiotic gut microbiota and a compromised intestinal barrier in the pathogenesis of hematopoietic failure[49,50]. In our retrospective study, all patients with SAA had imaging abnormalities that could reflect the presence of chronic inflammatory conditions and acute inflammatory damage. Five out of 17 recruited patients had imaging features suggestive of gastrointestinal involvement of tuberculosis infection[51].

The inflammatory stress-fueled antileukemic activities raise an interesting suggestion that patients with myeloid neoplasms who are either ineligible for intensive treatment or during maintenance therapy can be treated with immune-modulating agents such as recombinant inflammatory cytokines [52,53], immune checkpoint inhibitors[54], polyinosinic-polycytidilic acid (polyI:C)[55], and BCG vaccination[56]. Although inflammatory stress-fueled antileukemic activities benefit patient survival, an overwhelming infection can also be fatal. How to tip the balance between antileukemic activities and systemic inflammatory responses in the treatment of myeloid neoplasms with immune activating agents is another intriguing topic.

This study had several limitations. First, the mechanisms underlying inflammatory stress-induced hematopoietic failure were not further explored due to our limited knowledge and laboratory techniques. Second, the extrapolation of inflammatory stress-fueled antileukemic activities requires additional laboratory investigations to substantiate the validity. Third, the inflammatory response in the chest and abdomen lacked etiopathological diagnosis due to the contraindications of surgical intervention.

CONCLUSION

Aggravated inflammatory stresses can induce severe aplastic cytopenia in advanced MDS, resulting in the disease phenotypic transformation from a morphologically evidenced myeloid neoplasm to immune-mediated hematopoietic failure. In this process, both normal and malignant hematopoiesis were heavily suppressed with the preferential suppression of leukemic cells, raising the possibility of an antileukemic mechanism. Patients with myeloid neoplasms who are ineligible for intensive treatment or during maintenance therapy can be treated with immune-modulating agents. However, the benefit and fatal adverse effects should be carefully weighed.

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FOOTNOTES

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