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Tuberculosis-induced aplastic crisis and atypical lymphocyte expansion in advanced myelodysplastic syndrome: A case report and review of literature

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Abstract

BACKGROUND

Myelodysplastic syndrome (MDS) is caused by malignant proliferation and ineffective hematopoiesis. Oncogenic somatic mutations and increased apoptosis, necroptosis and pyroptosis lead to the accumulation of earlier hematopoietic progenitors and impaired productivity of mature blood cells. An increased percentage of myeloblasts and the presence of unfavorable somatic mutations are signs of leukemic hematopoiesis and indicators of entrance into an advanced stage. Bone marrow cellularity and myeloblasts usually increase with disease progression. However, aplastic crisis occasionally occurs in advanced MDS.

CASE SUMMARY

A 72-year-old male patient was definitively diagnosed with MDS with excess blasts-1 (MDS-EB-1) based on an increase in the percentages of myeloblasts and cluster of differentiation (CD)34+ hematopoietic progenitors and the identification of myeloid neoplasm-associated somatic mutations in bone marrow samples. The patient was treated with hypomethylation therapy and was able to maintain a steady disease state for 2 years. In the treatment process, the advanced MDS patient experienced an episode

of progressive pancytopenia and bone marrow aplasia. During the aplastic crisis, the bone marrow was infiltrated with sparsely distributed atypical lymphocytes. Surprisingly, the leukemic cells disappeared. Immunological analysis revealed that the atypical lymphocytes expressed a high frequency of CD3, CD5, CD8, CD16, CD56 and CD57, suggesting the activation of autoimmune cytotoxic T-lymphocytes and natural killer (NK)/NKT cells that suppressed both normal and leukemic hematopoiesis. Elevated serum levels of inflammatory cytokines, including interleukin (IL)-6, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), confirmed the deranged type I immune responses. This morphological and immunological signature led to the diagnosis of severe aplastic anemia secondary to large granule lymphocyte leukemia. Disseminated tuberculosis was suspected upon radiological examinations in the search for an inflammatory niche. Antituberculosis treatment led to reversion of the aplastic crisis, disappearance of the atypical lymphocytes, increased marrow cellularity and 2 mo of hematological remission, providing strong evidence that disseminated tuberculosis was responsible for the development of the aplastic crisis, the regression of leukemic cells and the activation of CD56+ atypical lymphocytes. Reinstitution of hypomethylation therapy in the following 19 mo allowed the patient to maintain a steady disease state. However, the patient transformed the disease phenotype into acute myeloid leukemia and eventually died of disease progression and an overwhelming infectious episode.

CONCLUSION

Disseminated tuberculosis can induce CD56+ lymphocyte infiltration in the bone marrow and in turn suppress both normal and leukemic hematopoiesis, resulting in the development of aplastic crisis and leukemic cell regression.

Key Words: Myelodysplastic syndrome; Aplastic crisis; Atypical lymphocyte; Leukemic cell regression; CD56+ lymphocyte expansion; Disseminated tuberculosis; Case report

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Core Tip: In patients with myelodysplastic syndrome, bone marrow cellularity and myeloblasts usually increase with disease progression. An advanced myelodysplastic syndrome patient experienced an episode of aplastic crisis. During the aplastic crisis, leukemic cells regressed. The bone marrow was infiltrated with atypical lymphocytes that expressed high frequencies of cluster of differentiation (CD)3, CD5, CD8, CD16, CD56 and CD57. Antituberculosis treatment led to reversion of the aplastic crisis, disappearance of the atypical lymphocytes, increased marrow cellularity and 2 mo of hematological remission, suggesting that disseminated tuberculosis was responsible for the development of aplastic crisis, regression of leukemic cells and activation of CD56+ cells.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a heterogeneous disease of hematopoietic progenitor cells (HPCs) resulting from malignant proliferation and ineffective hematopoiesis. Oncogenic somatic mutations and increased apoptosis, necroptosis and pyroptosis lead to the accumulation of earlier HPCs and impaired productivity of mature blood cells[1,2]. Morphologically, MDS is characterized by one or more lineages of dysplasia, and an increased percentage of myeloblasts is the most significant dysplastic feature[3,4]. The bone marrow in MDS patients is usually hyperplastic, consistent with dysregulated proliferation and differentiation. However, a fraction of MDS patients can be hypoplastic[5,6]. The identification of cytogenetic abnormalities and oncogenic somatic mutations, especially unfavorable ones, is helpful in the determination of leukemic hematopoiesis[1,2,5-7]. With regard to immunological signatures, patients with low-risk MDS, especially hypoplastic MDS, exhibit autoimmune-predominated responses resembling those in severe aplastic anemia

(SAA), whereas patients with advanced MDS demonstrate negative regulator-predominated immune exhaustion resembling that in acute myeloid leukemia (AML)[1,5,6]. An increased percentage of myeloblasts and the presence of unfavorable somatic mutations are signs of leukemic hematopoiesis and indicators of entrance into an advanced stage[2,3,4,6,7]. In MDS patients, bone marrow cellularity and the percentage of myeloblasts usually increase with disease progression[1,3,4], which is generally attributed to clonal evolution or immune escape *via* the acquisition and accumulation of novel oncogenic mutations under chronic immune pressure[2,7,8]. However, some patients, especially in the end stage, experience an episode of progressive cytopenia, usually concomitant with severe inflammatory conditions. In this situation, the bone marrow can be hypoplastic, leukemic clones are concealed, and the immunological signature changes from an exhausted phenotype to deranged autoimmune responses resembling those in autoimmune hematopoietic failure. Severe infections during aplastic crisis are generally ascribed to functional defects in the myeloid lineage and severe neutropenia[9-11].

A patient with definitively diagnosed MDS-EB-1 experienced an episode of aplastic crisis with concomitant infiltration of atypical lymphocytes and regression of leukemic cells in the bone marrow. The atypical lymphocytes expressed high frequencies of cluster of differentiation (CD)3, CD5, CD8, CD16, CD56 and CD57. Antituberculosis treatment led to not only reversion of the aplastic crisis but also disappearance of the atypical lymphocytes, increased marrow cellularity and 2 mo of hematological remission. This treatment response indicated that disseminated tuberculosis infection, especially gut involvement, was responsible for the development of the aplastic crisis, the regression of leukemic cells and the activation of CD56+ atypical lymphocytes. The reversible aplastic crisis suggested that autoimmune responses due to infectious diseases represent the major pathophysiology in patients with end-stage MDS. Leukemic cell regression during aplastic crisis and a short duration of hematopoietic remission following the resolution of infectious episodes suggest that autoimmune hematopoietic failure likely functions as an inflammatory stress-fueled antileukemic

mechanism; the relapse similar to that in transient "spontaneous remission" suggests that the inflammatory stress-fueled antileukemic activity is unable to eradicate the leukemic clones; and the genetically damaged HPCs, together with the active inflammatory condition, contribute to the development of autoimmune hematopoietic failure.

CASE PRESENTATION

Chief complaints

Aggressive pancytopenia for 4 weeks.

History of present illness

Two years earlier, a 72-year-old Chinese man sought medical help for gradually worsening fatigue and cytopenia. At that time, the complete blood cell count (CBC) showed the following results: White blood cells (WBCs), 1.44 × 10^9/L; absolute neutrophil count (ANC), 0.62 × 10^9/L; red blood cells (RBCs), 2.74×10^{12}/L; hemoglobin level (Hb), 97 g/L; platelets (Plts), 175 × 10^9/L; and absolute reticulocyte count (Ret), 44.62 × 10^9/L. He was diagnosed with MDS-EB-1 based on hypercellular bone marrow and an increased percentage of myeloblasts (accounting for 8.5% of all nucleated cells) on morphological evaluation, an increased percentage of CD34+CD33+ cells (6.82%) on immunotyping analysis, a normal 46,XY karyotype on cytogenetic analysis, and the identification of somatic mutations in *ASXL1*, *RUNX1*, *STAG1* and *N-RAS* genes on molecular analysis. In the following 2 years, the patient was treated with hypomethylation therapy [a total of 14 courses of decitabine (25 mg/d × 5 d)] as a solitary antileukemic agent and was able to maintain a steady disease state. Four weeks prior to this hospitalization, the patient's fatigue was aggravated, performance status deteriorated, and cytopenia significantly worsened. The degree of fatigue was far more severe than the degree of anemia.

History of past illness

The patient had a 6-year history of leukocytopenia prior to the diagnosis of MDS-EB-1. He denied having diseases affecting the cardiovascular, endocrine, respiratory, gastrointestinal, urogenital or musculoskeletal systems.

Personal and family history

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

Physical examination

The patient was 172 cm tall and weighed 63.5 kg. Upon admission, his vitals were as follows: Temperature, 36.4 ℃; respiratory rate, 18 breaths per minute; heart rate, 88 beats per minute; and blood pressure, 114/76 mmHg. Physical examination revealed the presence of mild tenderness of the right lower abdomen. No significant signs involving the nervous, respiratory, cardiovascular, or musculoskeletal systems were present.

Laboratory examinations

Routine laboratory examinations: At hospitalization, the CBC showed the following results: WBCs, 0.93 × 10^9/L; ANC, 0.34 × 10^9/L; RBCs, 1.57 × 10^{12}/L; Hb, 48 g/L; Plts, 16 × 10^9/L; Ret, 18.50 × 10^9/L; and C-reactive protein, 263.62 mg/L. The coagulation profile showed hyperfibrinogenemia (4.100 g/L), with a D-dimer level of 0.38 mg/L. Urine analysis revealed occult blood (2+) and protein (1+). Biochemical tests showed moderate hypoalbuminemia (26.1 g/L) and low serum levels of potassium (2.97 mmol/L), sodium (128 mmol/L) and chlorine (94 mmol/L), with the absence of abnormalities in markers of liver and renal function. Pathogenic cultures of blood samples were sterile. Immunological tests for hepatitis A, B, and C virus and human immunodeficiency virus were negative. Tests for Epstein-Barr virus and parvovirus B19 DNA were negative. The IFN-γ release assay yielded a positive result. The pleural effusion in aspirates was bloody, with an elevated level of adenosine deaminase. The

serum levels of IL-6, IFN-γ and TNF-α were elevated, suggesting the presence of deranged type I immune responses.

Specific laboratory examinations for blood diseases: A morphological evaluation was performed. The bone marrow became aplastic, with the appearance of sparsely distributed atypical lymphocytes that accounted for 77% of all nucleated cells (Figure 1). Of the atypical lymphocytes, the chromatin was highly concentrated, the cytoplasm was excessively abundant, with eosinophilic shade on the basophilic background and most prominently adjacent to the nucleoli without visible granules, and the membrane was canthous. Basophilic substances were present in the cytoplasm of almost all erythrocytes, suggestive of dysplasia in erythropoiesis. Notably, the leukemic cells disappeared. Immunotyping analysis of bone marrow samples revealed decreases in the frequencies of CD34 (0.24%) and CD19 (14.28%) expression and increases in the frequencies of CD3 (54.15%), CD5 (47.23%), CD8 (28.49%), CD16 (28.33%), CD56 (22.16%) and CD57 (41.91%) expression. The immunological signature indicated the activation and expansion of autoimmune cytotoxic T-lymphocytes (CTLs) and NK/NKT cells, resembling that in patients with "SAA" secondary to large granular lymphocyte leukemia (LGLL)[12,13]. The massively reduced frequencies of CD34 and CD19 expression indicated the exhaustion of HPCs and B lymphocytes. Next-generation sequencing analysis revealed a novel somatic mutation in the *KMT2D* gene in addition to the previously reported mutations. These laboratory data indicated the development of an "aplastic crisis", in which the activated CTLs and NK/NKT cells were likely responsible for the autoimmune suppression of normal and leukemic hematopoiesis.

Imaging examinations

Computed tomography (CT) scans were performed in the search for an inflammatory niche, and the chest (Figure 2) and abdominal (Figure 3) CT features, together with the IFN-γ release assay positivity and bloody pleural effusion, suggested a diagnosis of

disseminated tuberculosis involving the lungs, pleura, hilum, mediastinum, gastrointestinal tract, peritoneum and urinary tract[14,15].

FINAL DIAGNOSIS

The patient was diagnosed with SAA secondary to LGLL.

TREATMENT

The patient was tentatively treated with a combination of intravenous antibiotics [kanamycin (0.5 g/d) and levofloxacin (0.5 g/d) for 2 wk] for the inflammatory episode, antituberculotics [a combination of rifampicin (0.45 g/d), isoniazid (0.3 g/d), ethambutol (1.0 g/d), and pyrazinamide (1.0 g/d) for 2 mo and subsequently a combination of rifampicin and isoniazid for 6 mo] for the suspected tuberculosis infection, cyclosporine (100 mg bid) to repress the deranged cellular immune responses[16,17], and recombinant human granulocyte colony-stimulating factor (rhG-CSF) for the severe neutropenia. Supportive care was mandatory, without hemolysis or platelet transfusion refractoriness.

OUTCOME AND FOLLOW-UP

Three weeks of treatment led to significant improvement in the hematological parameters, disappearance of the expanded atypical lymphocytes, and an increased marrow cellularity. The patient's inflammatory symptoms were gradually ameliorated, and his performance status was significantly improved. The patient was released, and antituberculosis treatment was continued. One month after release from our hospital, he achieved hematological remission. CBC monitoring at the peak showed the following: WBCs, 4.72 × 10^9/L; ANC, 3.35 × 10^9/L; RBCs, 3.64 × 10^{12}/L; Hb, 137 g/L; and Plts, 281 × 10^9/L. This treatment response indicated that disseminated tuberculosis was responsible for the aplastic crisis, leukemic cell regression and atypical lymphocyte expansion. However, the hematological response lasted for only 2 mo, and cytopenia reemerged, with an increase in bone marrow cellularity and the percentage of

myeloblasts. Hypomethylation therapy was reinstituted. The patient had received 19 mo of hypomethylation therapy [a total of 3 courses of decitabine (25 mg/d × 5 d) and 10 courses of azacitidine (100 mg/d × 7 d)]. The disease phenotype transformed into AML during hypomethylation therapy. After the transformation, He denied further antileukemic treatment and eventually died of disease progression and an overwhelming infectious episode.

DISCUSSION

In this manuscript, we describe an episode of reversible aplastic crisis in a patient with advanced MDS. The patient was definitively diagnosed with MDS-EB-1 primarily based on an increase in the percentage of myeloblasts on morphological examination of bone marrow smears and slices and the identification of unfavorable somatic mutations in myeloid neoplasm-associated genes, the two most significant parameters in the diagnosis and risk stratification of MDS[1-4]. Initially, the bone marrow was hypercellular. With the development of an inflammatory episode during hypomethylation therapy, the bone marrow became aplastic, with the infiltration of morphologically atypical lymphocytes. Meanwhile, the leukemic cells regressed. Immunotyping analysis of the atypical lymphocytes revealed high CD3, CD8, CD5, CD16, CD56 and CD57 expression. Disseminated tuberculosis was suspected in the search for an inflammatory niche. Tentative treatment with antituberculotics resulted in the reversion of bone marrow cellularity, disappearance of atypical lymphocytes and reappearance of leukemic clones, providing strong evidence for disseminated tuberculosis as the contributor to the phenotypic transformations. This case study revealed the following attractive points:

The first attractive point of this case study is that active tuberculosis infection can trigger bone marrow-predominated autoimmunity in patients with advanced MDS, inducing an episode of aplastic crisis. In this patient, aplastic crisis developed during an inflammatory condition, and autoimmune pathogenesis predominated in the bone marrow. Organ-specific autoimmunity suggests that the targeted antigens are located in

the bone marrow. Antituberculosis treatment reversed the marrow-predominated autoimmunity, providing strong evidence that active tuberculosis was responsible for the development of the aplastic crisis. The relief of hematopoietic suppression after successful treatment of the underlying infection suggested that the autoimmune hematopoietic failure was fueled by inflammatory stresses. Tuberculosis-associated aplastic cytopenia has been reported in a few studies[18-22]. Tuberculosis-associated aplastic cytopenia has even been reported in Bacillus Calmette-Guerin vaccination[23]. Tuberculosis infection can trigger cellular immune responses and lead to the excessive production of proinflammatory cytokines[24,25], thereby inducing immune-mediated hematopoietic injury[26,27]. Gut involvement of tuberculosis infection likely plays a more important role because tuberculosis-induced aplastic cytopenia has been reported merely in disseminated tuberculosis instead of isolated pulmonary tuberculosis. Gastrointestinal tuberculosis induces not only inflammatory lesions of its own but also gut dysbiosis, resulting in increased epithelial permeability and compromised barrier function in infected and downstream intestinal segments[28,29]. The gastrointestinal tract is an organ that hosts the most abundant lymphatic tissues and microbial community and therefore can provide sufficient activated immune cells and continuously supply exogenous antigens from both pathogenic and commensal microbes to initiate and perpetuate deranged autoimmunity in the context of increased epithelial permeability and gut inflammatory conditions[30-33], leading to autoimmune hematopoietic failure[34-37]. In our retrospective study to explore the inflammatory conditions of SAA patients during inflammatory flare-ups, 5 of 17 recruited patients exhibited imaging abnormalities suggestive of tuberculosis infection, all involving the gastrointestinal tract and suggesting a high frequency of tuberculosis infection in autoimmune hematopoietic failure[38]. Gut inflammatory conditions in the sustenance of autoimmune responses have been demonstrated by the fact that the onset of an autoimmune disease cannot occur in a germ-free state[39-41].

The second attractive point is that active tuberculosis infection can induce CD56+ lymphocyte proliferation. The concentrated chromatin, abundant cytoplasm, canthous

membrane and eosinophilic shade indicated that the lymphocytes were activated. Immunological analysis confirmed that the atypical lymphocytes were activated autoimmune CTLs and NK/NKT cells. The disappearance of atypical lymphocytes with reversion of the aplastic crisis following antituberculosis treatment provided convincing evidence that tuberculosis infection activated CTLs and CD56+ cells. It is reasonably concluded that active tuberculosis stimulated CD56+ cell expansion and in turn suppressed normal and leukemic hematopoiesis. NK and NKT cells are important effector cells in the defense against tuberculosis infection, and tuberculosis antigens can directly stimulate NK/NKT cell proliferation[24,25]. Activated NK/NKT cells can suppress host hematopoiesis *via* secretion of excessive hematopoietic inhibitors, resulting in autoimmune hematopoietic failure[12,13]. However, in patients with SAA secondary to LGLL, tuberculosis is seldom considered the original trigger. More interestingly, visible granules were absent from the activated CD56+ cells, which is distinctive from LGLL with respect to morphology.

The third attractive point is that the leukemic clones were concealed during aplastic crisis, and following antituberculosis treatment, the leukemic clones reemerged after a short duration of hematological remission. This finding suggests that tuberculosis-induced autoimmunity suppressed both normal and leukemic hematopoiesis, with preferential suppression of leukemic cells[42-44]. Neoplasm-associated antigens or damage-associated molecular patterns on genetically defective HPCs likely initiate the primary inflammatory niche in the bone marrow environment and determine organ specificity[45-47]. However, engagement of an exogenous stimulation is critically required in the induction of autoimmune hematopoietic failure[48-50]. Inflammatory stresses due to disseminated tuberculosis fuel organ-specific autoimmunity, resulting in the development of an aplastic crisis. In this sense, autoimmune hematopoietic failure may function as an antileukemic mechanism[51], and disseminated tuberculosis may strengthen immune surveillance against malignant proliferation. However, the leukemic clones cannot be eradicated, resulting in relapse after a short duration of hematological remission following antituberculosis treatment, similar to the process of

transient "spontaneous remission"[52,53]. Chronic autoimmune hematopoietic failure is likely caused by inflammatory stress-fueled antileukemic activities targeting genetically damaged HPCs in the context of an active chronic inflammatory condition. We previously reported a patient with refractory SAA who progressed to a myelodysplastic/myeloproliferative neoplasm during the consecutive administration of gut-cleansing preparations (GCPs) and microbiota-modulating treatments[54], but prior intermittent GCPs achieved several cycles of hematopoietic recovery and disease relapse without evident leukemic cell expansion[55]. These data indicated that inflammatory stresses rather than a specific infection fuel organ-specific autoimmunity[34,45,48,50,56].

Limitations of the case study include the lack of an etiopathological diagnosis for disseminated tuberculosis and lack of identification of proinflammatory inhibitors. In addition, the clonality of the atypical lymphocytes was not determined.

CONCLUSION

Taken together, the results of this case study show that disseminated tuberculosis infection can stimulate the activation and expansion of CD56+ cells and that activated CD56+ cells can suppress both normal and leukemic hematopoiesis, resulting in aplastic crisis and leukemic cell regression in advanced MDS. Antituberculosis treatment can reverse autoimmunity. This inflammatory stress-fueled autoimmunity may represent an antileukemic mechanism, which could be helpful in elucidating the pathogenesis of autoimmune hematopoietic failure and immunological treatments for myeloid neoplasms. Disseminated tuberculosis infection, especially gut involvement, should be given particular attention in autoimmune hematopoietic failure.

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