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A Case Report and Literature Review of Senile Myelodysplastic Syndrome with Mast Cell Hyperplasia

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Abstract

Myelodysplastic Syndrome (MDS) is a group of blood system-derived malignant clonal diseases that mostly affect the elderly population. The main clinical manifestations of MDS are peripheral blood cell reduction, bone marrow morbid hematopoiesis with or without an increase in bone marrow primitive naive cells, and a high risk of transformation to acute leukemia. The prognosis of MDS in elderly people is relatively poorer. Mast cell hyperplasia is manifested as mast cell infiltration, accumulation, and damage to one or more organs of the human body, such as the bone marrow, skin, or digestive tract, is rare in MDS patients. In addition, it is unknown if gene mutations in MDS trigger the mast cell hyperplasia or whether mast cell hyperplasia affects MDS. Here, we reported a case of MDS with mast cell hyperplasia in an 87-year-old man and reviewed the related literature to discuss the underlying interactions.

Keywords: MDS; Mast cell hyperplasia; Elderly population

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Introduction

Myelodysplastic Syndrome (MDS) is a clonal malignant disease originating from multifunctional hematopoietic stem cells that usually affects elderly population, and the incidence gradually increases with the age. At the early stage, MDS is often manifested as excessive apoptosis of bone marrow hematopoietic stem cells, ineffective hematopoiesis and differentiation, and maturation disorders. At the middle stage, malignant clonal primordial cells proliferate and increase in MDS, having an increased risk in transformation to leukemia routine blood test in MDS is usually shown as anemia, leukopenia, and/or thrombocytopenia while the clinical symptoms are often characterized by anemia, dizziness, fatigue and so on. However, due to the insidious onset, clinical missed diagnosis and misdiagnosis of MDS often occur which delays the disease treatment and affects the prognosis. Moreover, the elderly population was more likely to have various underlying medical conditions, and weak immunity, which makes them more vulnerable to MDS, and bring worse prognosis, and can lead to death [1]. Besides, MDS is more often complicated with immune disorders such as arthritis, vasculitis, and autoantibody defects, but its cause remains unclear [2]. Mast cells, regarded as the effector cells of the allergic reaction, are also closely related to immune abnormalities, playing an important role in the early and acute stages of the allergic reaction. However, cases of MDS with mastocytosis are rare and the mechanism is obscure. In this paper, a case of senile MDS with mastocytosis was reported and literature reviewed.

Case Presentation

The patient, a male aged 87 years old, was hospitalized on September 17th, 2020, mainly due to leukopenia for four years, fatigue for more than one year, and precordial pain for two days. In August 2016, the patient had noticed a slight decrease in white blood cells (WBC, 3.46 × 10^9/L), but without fever, chest pain, fatigue, or other discomforts. After oral administration of leukopenia drug Diyushengbai tablets, the number of WBC increased to more than 4.0 × 10^9/L. However, after the drug withdrawal, the number of decreased again. Since then, the patient visited doctors and orally take a variety of leukopenia drugs, such as burnet root leukopoietic tablets and *Astragalus* gum leukopoietic capsule. Which were effective at the beginning, but gradually became ineffective. In July

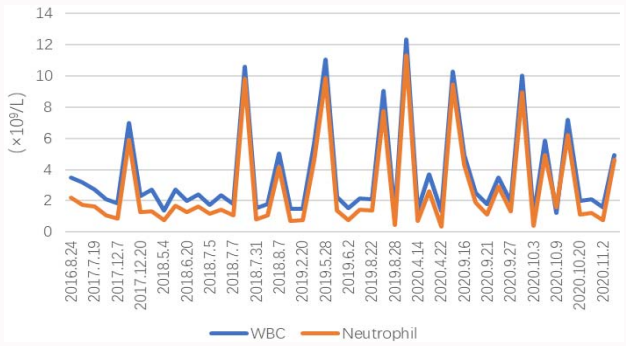

Figure 1: Variation in blood count WBC (× 10^9/ L) and neutrophil (NEUT) absolute value (× 10^9/ L) greater than 10 × 10^9/L period to consider infection-related.

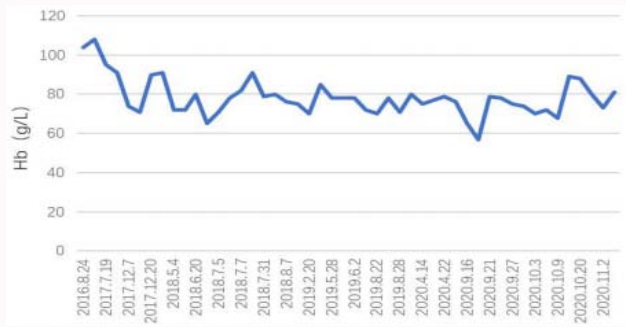

Figure 2: A gradual downward trend of hemoglobin Hb (g/L).

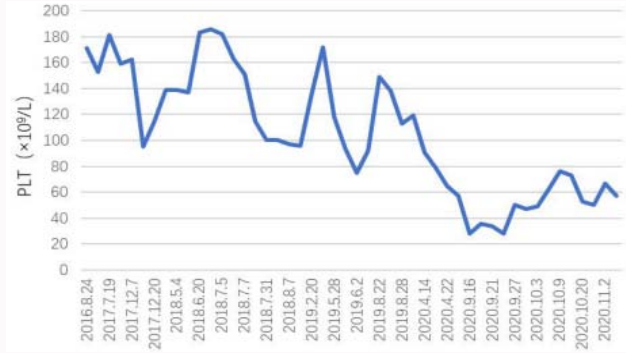

Figure 3: A gradual downward trend of platelet PLT (× 10^9/L).

2018, anemia emerged and the bone marrow morphology indicated that there were fewer nucleated cells with erythropoiesis and small cell hypochromic changes, cytochemical NAP(-), HS(-); MDS mutant genes were negative, while bone marrow biopsy suggested extremely low hyperplasia. Based on the above results, "leukopenia, mild anemia" was diagnosed, and recombinant human granulocyte colony-stimulating factor (150 ug for subcutaneous injection) was prescribed once a week. Consequently, the prescription sustained a WBC count of about 4.0 × 10^9/L. Therapy for anemia, including supplement iron and other hematopoietic raw materials, was nearly ineffective. In February 2019, the patient developed dizziness, fatigue. Routine blood test showed significantly low WBC (1.48 × 10^9/L, neutrophils 0.68 × 10^9/L), and moderate anemia (RBC 2.63 × 10^{12}/L, Hb 70 g/L). Subsequently, the patient had received long-term treatment of leukopenia drugs, infusion of red blood cells, and Erythropoietin (EPO). On September 15th, 2020, precardiac pain complicated with asthma, shortness of breath, and panic showed up and lasted for about half an hour without obvious causes. Blood tests showed: WBC 1.40 × 10^9/L, Hb 69 g/L, and PLT 32 × 10^9/L. The electrocardiogram examination showed sinus tachycardia, II, III, aVF qrs, qr type, and ST-T change, but there was no apparent abnormality in the myocardial enzyme spectrum. Then the patient was hospitalized with leukopenia. The admission physical examination indicated that the patient's body temperature was 36.3°C, pulse was 84/min, respiration was 18/min, and blood pressure was 143/62 mmHg. The patient was alert, cheerful, and had severe anemia. He had a bleeding point across his body, but his superficial lymph nodes were not swollen. His skin and mucous membranes were clear of yellow stains. There was no tenderness in the sternum, no anomalies in the heart or lungs, and no contact with the liver or spleen at the subcostal stage. The patient's blood test after admission showed WBC 2.53 × 10^9/L, PLT 36 × 10^9/L, RBC 2.4 × 10^{12}/L, Hb 57 g/L, and MCV 82.9 fl. Anemia was corrected by infusion of red blood cells, while Thrombopoietin (TPO) was used to increase platelets. Cardiac dual-source CT examination only revealed mild stenotic lesions in multiple blood vessels. Paroxysmal precardiac pain was relieved when anemia was corrected. During hospitalization, the patient often developed paroxysmal asthmatic symptoms. A check at his medical history indicated that in the past two years, when leukocytopoiesis drugs and other medications were used simultaneously, the patient had developed asthma, shortness of breath, increased heart rate, and other asthma-related symptoms, including a longer period of headache. These symptoms were relieved by antispasmodic and antiasthmatic drugs. A pulmonary function test revealed mild obstructive ventilation dysfunction and a negative relaxation test, ruling out paroxysmal asthma as asthma and pointing to an allergic reaction as the cause of airway hyper-responsiveness. The above symptoms could be prevented by separating the leukocytopoiesis drug use from other medications. At the same time, the patient was experiencing severe skin itching symptoms with no visible rashes, and a variety of anti-allergic drugs were ineffective. After the above treatment, the patient's clinical symptoms were partly relieved, but the routine blood tests disappointing appeared progressing, from early leukopenia (Figure 1) to progressive anemia (Figure 2) and then to thrombocytopenia (Figure 3). Bone marrow puncture and biopsy performed after admission revealed aggressive hyperplasia, degenerated cells, granulocyte accounted for 50.4% of total cells, primitive cell ratio of 8%, increased early and young granulocyte ratio, and a few middle and young granulocytes with development imbalance and degenerative changes in the nuclear pulp. Erythroid cell accounted for 40% of the cells, the proportion of middle and late-young red cells increased, and some cells were small and the edge of their cytoplasm was irregular. Binuclear young erythrocyte, basophilic stippling, Hao Zhou's corpuscles, megaloblastic changes, and metatypical erythrocytes (tears, target shape) could be observed. In total there were 34 megakaryocytes, with 20 of them being classified as 16 granular, two plates, and two bare karyotypes. Cellular chemistry shows NAP (-), HS (-). Bone marrow pathology indicated that bone marrow hyperplasia was active and the erythropoiesis was dominant, especially in the middle and late stages of the red blood cell cycle. Reduction of megakaryocyte and grain ratio without anomalies in distribution. Hyperplasia of mast cells, scattered or clustered, is diffused in some area (Figure 4). MDS-related genetic mutations of bone marrow cells were detected by flow cytometry, the result suggested mutations of BCORY156fs, STAG2S1058X, ASXL1Q778X, BCORY304fs, U2AF1S34F, DNMT3AR882C, and TET2Q1030R were positive, while Chromosome 46, XY, no abnormal karyotype; BCR/ABL detected by Fluorescence *In Situ* Hybridization (FISH)

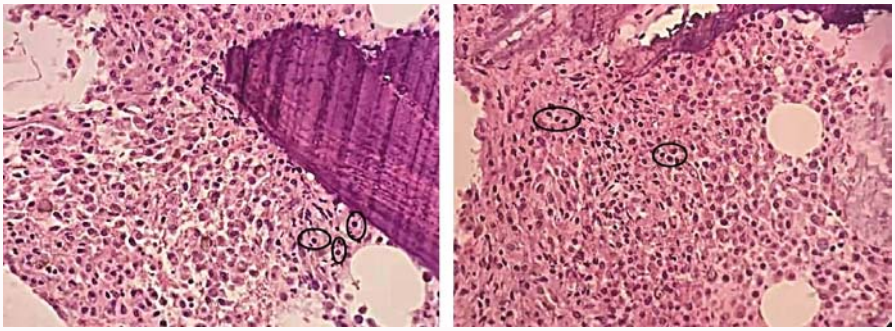

Figure 4: A bone marrow biopsy showed active erythroid hyperplasia, with increased mast cell infiltration (as shown by black circle), large nucleus, loose chromatin, smooth surface of cell body and its long processes (HE×100).

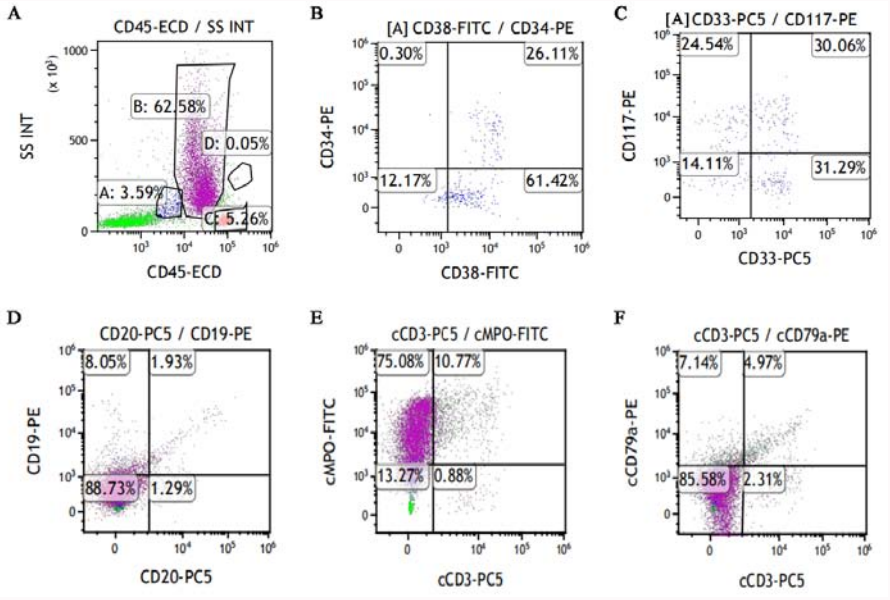

Figure 5: Subgroup of the patient's bone marrow cells detected by flow cytometry.
A) CD45/SSC scatter map of the bone marrow cells: The immature cells in zone A accounted for 3.59%, the neutrophils in zone B accounted for 62.58%, the lymphocytes in zone C accounted for 5.26%, mononuclear cells in zone D accounted for 0.05%.
B) CD38/CD34 scatter diagram shown after gating the naive cells in A. CD34 + naive cells account for 0.3% of all naive cells and no abnormal cell subsets detected in naive cells.
C) The CD33/CD117 scatter diagram shown after gating the naive cells in A. No abnormal cell subsets detected in naive cells.
D) CD20/CD19 scatter plots of patient bone marrow cells without a gate. No abnormal cell populations detected.
E) cCD3/cMPO scatter plots of patient bone marrow cells without a gate. No abnormal cell populations detected.
F) cCD3/cCD79a scatter plots of patient bone marrow cells without a gate. No abnormal cell populations detected.

was negative. No abnormal cell subsets immunophenotype had been detected by flow cytology (Figure 5). The mast cell hyperplasia-related genes were negative; therefore the patient was diagnosed as myelodysplastic syndrome with mast cell hyperplasia.

Due to poor physical condition and low willingness to treat, the patient did not receive demethylation therapy or other radical regimens except for blood transfusion, EPO, TPO, cyclosporine, thalidomide, ossification triol, and system supportive medication. After the treatment, the patient's WBC was maintained at more than 2.0×10^9/L, Hb maintained at around 80 g/L, PLT maintained at around 50×10^9/L, the general condition promoted and the blood transfusion intervals time was significantly prolonged.

Discussion

MDS diagnosis and treatment

The pathogenesis of MDS is still unknown, but recent research had focused on the disease epigenetic changes, gene mutations, and heterozygosity deletion. In most patients, it is thus straightforward to diagnose MDS on the basis of WHO criteria. However, in many cases with cytopenia(s), it may be quite difficult to establish (or exclude) the diagnosis MDS. These may be patients without a cytogenetic abnormality and only mild cytopenia, patients with a typical karyotype and cytopenia but only slight or absent dysplasia, or patients with transfusion-dependent macrocytic anemia without karyotype abnormalities and without diagnostic dysplasia. The most frequent somatic mutations driving age-related clonal expansions, and the biologic mechanism involved in the transition from clonal hematopoiesis to myeloid neoplasm, including clonal selection and evolution [3-4]. On accounting of the recent advances in epidemiology, genetics, molecular biology, new diagnostic methods, and the discovery of molecular markers have enhanced our understanding of MDS. The current classification approach adopted by the WHO is based on a combination of morphology, immunophenotype,

and genetic features to define distinct clinicopathologic disease entities, independently from the underlying causes that are often unknown. According to this principle, the diagnosis of MDS lies on 2 hallmarks, the evidence of myelodysplasia and the proof of clonal hematopoiesis. Diagnostic and classification criteria of myeloid neoplasms with myelodysplasia. The diagnostic approach to MDS includes morphologic studies of peripheral blood and bone marrow aspirate smears to evaluate abnormalities; bone marrow biopsy to assess marrow cellularity, topography and fibrosis; and cytogenetics to identify nonrandom chromosomal abnormalities. Additional investigations are also recommended, including flow cytometry immunophenotyping and Fluorescence *In Situ* Hybridization (FISH) [5]. The patient in the current case met one of the prerequisites, which was the presence of persistent tricline hemocytopenia for at least one year. Bone marrow puncture showed that the blast cells were significantly increased but did not reach 20%. The pathological erythropoiesis was obvious, and blast cells were also found in bone marrow biopsy. Methylation gene mutations that closely related to MDS, such as BCORY156fs, STAG2S1058X, ASXL1Q778X, BCORY304fs, U2AF1S34F, DNMT3AR882C, and TET2Q1030R were found by using combined gene detection therefore the diagnostic MDS was established. MDS is a heterogeneous disease, and MDS patients are generally older with varying treatment intentions therefore the treatment should be individualized. At present, allogeneic hematopoietic stem cell transplantation is still the only possible way to cure the disease, but due to the limited HLA matching donor sources, patient physical score, basic disease, age, prognostic risk, or other factors, the elderly patients are generally not qualified for the transplantation. The treatment aim for most elderly patients is to improve cytopenia and the quality of life while delaying the progression of the disease. Treatment strategies, such as transfusion-supported symptomatic treatment, iron supplement and cytokines therapy, improvement of bone marrow hematopoietic microenvironment, and demethylation drug therapy, should be adapted to non-strengthening and risk assessment (IPSS/R score). Among those, demethylation therapy is important and beneficial, but due to the significant individual differences, bone marrow suppression time after treatment varies a lot, and there is a risk of severe infection and bleeding, which need to be concerned.

Mast cell hyperplasia

Mast Cells (Mast Cells: MCs) are essential immune cells in the human body, derived from CD34 precursor cells in the bone marrow. They are widely distributed in tissues, especially in the skin, respiratory mucosa or gastrointestinal tract, and are considered as effector cells of allergic reactions, especially in the early and acute stages of IgE- mediated allergic reactions. Mast cells are composed of heterogeneous cell groups that can secrete a variety of bioactive factors and affect many physiological processes. Their maturation and phenotypic function are influenced by their microenvironment, which releases a number of bioactive mediators that influence their unique recognition and reaction to various stimuli [6-7]. In the current case, the patient developed anaphylaxis as the disease progressed. The hyperplasia of mast cells in the bone marrow was thought to be linked to MDS, abnormal hematopoietic stem cells differentiation and gene mutation, and changes in the hematopoietic microenvironment in the bone marrow. However, the specific mechanism requires further investigation. Mastocytosis is characterized by the hyperplasia of clonal, immature, or atypical mast cells. In addition to traditional mast cell markers, activation point mutations at codon KIT (c- KIT) 816 could be detected, and abnormal CD25 or CD2 could be expressed [8]. Mastocytosis can also cause multiple clinical symptoms. The most common manifestations are wind-like skin rash and itching, other symptoms such as fatigue, abdominal pain, headache, hypotension, weight loss, tachycardia, dyspnea and sore muscles [9]. Severe cases can lead to multiple organ failure. Pathogenesis of mastocytosis is closely related to a mutation in the KIT gene [10]. In our case, bone marrow pathology showed that mast cells were proliferated, dispersed, or clustered, and diffused in some areas. Nonetheless, no KIT gene mutation was identified in the genetic detectation, and no obvious abnormal mast cell cloning was found in the flow cytology. Therefore, the case was not diagnosed as MDS complicated not with mastocytosis but with the mast cell hyperplasia, which is a rare case. Some studies retrospectively analyzed the mutation genes of MDS with systemic mastocytosis, and found that TET2 and ASXL1 genes mutation have nearly 50% Variant Allele Frequency (VAF), which indicates that almost all bone marrow cells may co express these mutations in a heterozygous state, suggesting that MDS and mastocytosis may have a common pathogenesis and a common cell origin [11-12]. However, in this case, further investigations are needed to determine whether MDS and mast cell hyperplasia are independent or have any potential relationship.

Treatment for MDS with mast cell hyperplasia

At present, there are no normative and specific treatment for the elderly MDS patients complicated with mast cell hyperplasia. However, demethylation therapy may play an important role in low-risk patients, and decitabine or azacytidine therapy can improve the prognosis and prolong the survival time of the patients. High-risk patients may be treated with a combination of other treatments depending on the physical fitness score of the patient and underlying diseases [13]. Additional immunosuppressive regulatory treatments such as cyclosporine or lenalidomide/thalidomide may also be effective to relatively low-risk patients. There was a study suggesting that lenalidomide could improve the status of anemia and amend the molecular genetic abnormalities [14]. Patients with mast cell hyperplasia have a high incidence of allergic reactions (up to 20~49 percent) [15], in which IgE is a major factor. The main inducers are Hymenoptera insects, some food, and drugs [16]. Omalizumab is a drug usually used to treat stubbornness and can reduce the mast cell activity and reactivity therefore the IgE-mediated allergic reactions [17]. Thus Omalizumab can be used in patients who have a poor response to the traditional treatment, but it cannot reduce the number of the mast cells. The patient failed to use demethylation drugs; he was therefore immunomodulated on the basis of supporting symptomatic therapy due to his old age and complex basic diseases. The WBC was maintained at more than 2.0×10^9/L, the Hb fluctuated around 80 g/L, the blood transfusion time was obviously prolonged, the PLT fluctuated around 50×10^9/L, the symptoms improved, and the patient was discharged. Continuous follow-up indicated that he was generally in good condition. In this complex case, we should avoid being too radical in treatment and instead choose an individualized treatment plan to enhance the quality of life and prolong survival time. Further research is needed on the progression, prognosis, and detailed pathogenesis of bone marrow. Due to the old age and complex underlying diseases, the patient could not be treated with demethylation drugs. On the basis of supporting symptomatic therapy, the patient was given immunomodulatory therapy and discharged after his condition was stabilized. Based on this case, we suggest that in order to improve the prognosis and the life quality of

elderly patients of this kind, we should avoid radical treatment but choose individualized treatment scheme concerning the pros and cons. Moreover, the progress, prognosis and detailed pathogenesis of bone marrow disease need further study.

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