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Coexistence of Multiple Myeloma, Mast Cell Hyperplasia, and Low-Level Myeloid Blastocytosis: A Report of a Rare Case

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Conflict of interest: None declared

Patient: Female, 73-year-old
Final Diagnosis: Low-level myeloid blastocytosis • mast cell hyperplasia • multiple byeloma
Symptoms: epistaxis • muscle pain • severe asthenia
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: Mast cell hyperplasia can present as systemic mastocytosis (SM) or reactive mast cell hyperplasia. Distinguishing between these 2 diseases is a critical challenge. Here, we report a rare case of concurrent mast cell hyperplasia, multiple myeloma (MM), and low-level myeloid blastocytosis. The potential mechanisms underlying the coexistence of the aforementioned 3 diseases were also analyzed.

Case Report: A patient with muscle pain was initially diagnosed with monoclonal gammopathy of undetermined significance (MGUS). Three years later, she progressively developed pancytopenia and renal function impairment. Three populations of abnormal cells were found in the bone marrow (myeloma cells 10.5%, myeloid blasts 0.18%, and mast cells 10%). Bone marrow biopsy (BMB) showed a single focal mast cell aggregate (>15 cells) with no multifocal dense infiltrates. Tryptase testing and KIT D816V mutation analysis results were negative. CD25 and additional KIT gene sequencing were not performed. Finally, she was diagnosed with multiple myeloma (MM), mast cell hyperplasia, and low-level myeloid blastocytosis.

Conclusions: This association among MM, mast cell hyperplasia, and low-level myeloid blastocytosis could either arise from abnormal stem cells of a common origin or result from one disease indirectly inducing or accelerating the progression of the other. Comprehensive immunophenotyping (including CD117, CD2, CD30, and CD25) and KIT mutation analysis are necessary to differentiate reactive mast cell hyperplasia from both systemic mastocytosis (SM) and SM with an associated hematologic neoplasm (SM-AHN). Positive expression of CD2, CD25, or CD30 together with KIT mutation may indicate SM or SM-AHN, and additional diagnostic criteria are required to confirm the diagnosis. If all the above test results are negative, reactive mast cell hyperplasia can be considered. More mechanistic evidence and similar cases are needed to better understand complex multilineage dysplasia.

Keywords: Multiple Myeloma • Mast Cell Hyperplasia
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Introduction

It is widely recognized that mast cells originate from pluripotential hemopoietic stem cells in the bone marrow, and their migration and differentiation subsequently rely on various cytokines, especially stem cell factor (SCF) and the SCF receptor KIT [1]. Mastocytosis can be divided into systemic mastocytosis (SM) and reactive mast cell hyperplasia [2]. Since 2022, SM has been categorized into 6 subtypes according to the WHO classification: bone marrow mastocytosis (BMM), indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), mast cell leukemia (MCL), and SM with an associated hematologic neoplasm (SM-AHN) [3]. Most (>90.0%) patients with SM carry the KIT D816V mutation in the tyrosine kinase domain of KIT, whereas other KIT mutations are present in a smaller percentage (1.0% to 4.0%) of patients [4]. SM is relatively common in myeloid malignancies, such as chronic myelomonocytic leukemia (CMML) [5], where the cytokine-rich microenvironment can drive mast cell hyperplasia. In contrast, it is rare in lymphomas and plasma cell neoplasms. In addition to SM, mast cells can be increased in the form of reactive mast cell hyperplasia in chronic inflammation, various hematologic disorders, and malignant neoplasms [6]. It is not easy to distinguish SM from reactive mast cell hyperplasia based solely on the quantity of mast cells in aspirate smears. In most cases, we can differentiate the forms of mast cell hyperplasia based on morphology, immunostaining, and KIT mutation status (**Figure 1**) [7]. The diagnosis of reactive mast cell hyperplasia is considered only when SM is excluded. In other words, reactive mast cell hyperplasia is essentially a diagnosis of exclusion. For reactive mast cell hyperplasia, SCF promotes mast cell survival via inactivation of the FOXO3a transcription factor, and downregulates and phosphorylates its target—Bim—a pro-apoptotic protein [8]. IL-4 induces the proliferation of mast cells by inducing leukotriene C4 synthase (LTC4 S) and cysteinyl leukotrienes (cys-LT) generation [9]. In these scenarios, mast cells exhibit only quantitative elevation, and KIT mutations are generally negative. Reports on reactive mast cell hyperplasia are exceedingly rare, and the pathogenesis and prognosis of reactive mast cell hyperplasia coexisting with hematologic disorders remain poorly understood. This gap highlights a significant unmet need to understand the pathophysiological links between mastocytosis and hematologic disorders. Here, we report the case of a patient who presented with multiple myeloma (MM), mast cell hyperplasia, and low-level myeloid blastocytosis. The potential mechanisms underlying this coexistence were also analyzed.

Case Report

Initial Presentation

In 2021, a 73-year-old female patient with muscle pain and a history of diabetes mellitus, hypertension, and rheumatoid arthritis (RA) came to a local clinic. A routine blood examination revealed that the white blood cell (WBC) count was 14.97 (4.00-10.00)×10^9/L, the neutrophil count was 11.15 (1.80-6.30)×10^9/L, the monocyte count was 1.58 (0.12-0.80)×10^9/L, the erythrocyte count was 2.49 (3.50-5.50)×10^{12}/L, the hemoglobin level was 70.0 (110.0-150.0) g/L, and the platelet count was 751 (100-300)×10^9/L. The immunoglobulin G level increased to 34.4 (7.0-16.6) g/L, the β2-microglobulin level increased to 5.49 (0.00-8.00) mg/L, the immunoglobulin κ light chain level decreased to 1.52 (1.70-3.70) g/L, the immunoglobulin λ light chain level significantly increased to 8.88 (0.90-2.10) g/L, and the κ/λ ratio decreased to 0.17 (1.35-2.65). Serum electrophoresis and immunofixation revealed the presence of a monoclonal IgG-λ paraprotein. The bone marrow aspirate (BMA) revealed trilineage hematopoiesis with maturation and abnormal plasma cells, which accounted for 9% of all cells. A total of 30 megakaryocytes were identified on the slide, including 2 granular megakaryocytes, 26 platelet-producing megakaryocytes, and 2 naked megakaryocytes. Platelets were scattered. No classic evidence for myeloproliferative neoplasm (MPN), including megakaryocytic proliferation or morphologic alterations, were identified. Flow cytometry revealed that abnormal plasma cells were positive for CD38, CD56, and CD138. The

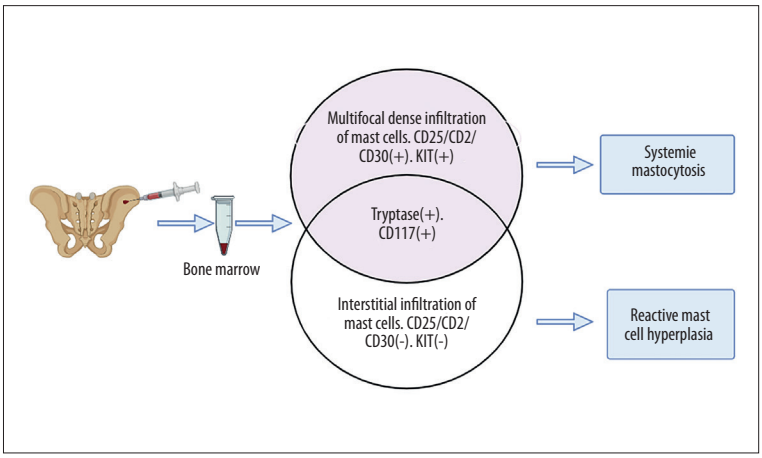

Figure 1. The differential diagnosis of SM and reactive mast cell hyperplasia in bone marrow biopsy. Systemic mastocytosis (SM) can be differentiated from reactive mast cell hyperplasia by immunophenotypic markers and multifocal dense infiltrates of mast cells in bone marrow biopsy. SM includes multifocal dense infiltration of mast cells, CD25/CD2/CD30 (+) and KIT (+). In contrast, reactive mast cell hyperplasia includes interstitial of mast cells, CD25/CD2/CD30 (-) and KIT (-). Both had positive expression for CD117 and tryptase.

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Table 1. Comparison of tests between 2021 (MGUS) and 2024 (MM) for this patient. Changes and comparisons of the main laboratory parameters and clinical symptoms related to plasma cell diseases in this patient.

		2021 (MGUS)	2024 (MM)
Blood tests		Elevated WBC and platelet counts, decreased RBC count	Pancytopenia
IgG		34.4 g/L	34.9 g/L
CRAB features	(1) C: hypercalcemia	No	No
	(2) R: renal failure	No	Yes
	(3) A: anaemia	No	Yes
	(4) B: bone lesions	No	No
SLiM features	(1) S: Sixty plasma cells	No	No
	(2) Light chain ratio ≥100	No	No
	(3) MRI focal lesions	No	No
Diagnosis		MGUS	MM

Table 2. Comparison of laboratory tests between 2021 (initial presentation) and 2024 (re-evaluation) for this patient.

	Initial presentation (2021)	Re-evaluation (2024)
Routine blood examination	Elevated WBC and platelet counts, decreased RBC count	Pancytopenia
Renal function	Normal	Creatinine 144.4 μmol/L, eGFR 31.0 mL/min
BMA/BMB	Plasma cells accounted for 9%	Plasma cells accounted for 10.5%, and mast cells accounted for 10%
Flow cytometry	Abnormal plasma cells: CD38 (+), CD56 (+), CD138 (+).	Abnormal plasma cells: were positive for CD38 (+), CD56 (+), and CD138 (+). Myeloid blasts: CD38 (+), CD13 (+), CD45 (+). Mast cells: CD117 (+), CD2 (-), CD30 (-).
Mast cell-specific studies	Not tested	Serum tryptase: 19.1 ng/mL KIT D816V mutation: negative
Diagnosis	MGUS	MM, mastocytosis, and myeloid blasts

WBC: White Blood Cells. RBC: Red Blood Cells. eGFR: estimated Glomerular Filtration Rate. BMA: Bone Marrow Aspirate. BMB: Bone Marrow Biopsy. MGUS: Monoclonal Gammopathy of Undetermined Significance. MM: Multiple Myeloma.

antinuclear antibody (ANA), rheumatoid factor, antistreptolysin O (ASO), and 25-hydroxyvitamin D3 levels were within normal limits. Splenomegaly was not confirmed with abdominal ultrasound. There was no sign of CRAB or SliM evidence (as shown in Table 1) for this patient [10]. Finally, she was diagnosed with monoclonal gammopathy of undetermined significance (MGUS) according to the International Myeloma Working Group (IWMG). Considering that her bone pain might be related to RA, the clinician prescribed tripterygium glycosides and methotrexate.

Follow-Up

Due to poor compliance, the patient could not provide any medical records, laboratory test results, or imaging study findings when she came to the clinic 3 years after her last visit, so the follow-up data from 2021 to 2024 was incomplete. The patient reported progressive weakness and decreased appetite over the past 3 years.

Disease Progression

In January 2024, the patient came to the clinic of the Provincial Hospital Affiliated with Shandong First Medical University due to severe asthenia and epistaxis. Laboratory tests revealed that the WBC count was 0.85×10^9/L, the erythrocyte count was 2.34×10^{12}/L, the hemoglobin level was 74 g/L, and the platelet count was 14×10^9/L. ASO, rheumatoid factor, and ANA were within the normal range, which indicated the RA was stable.

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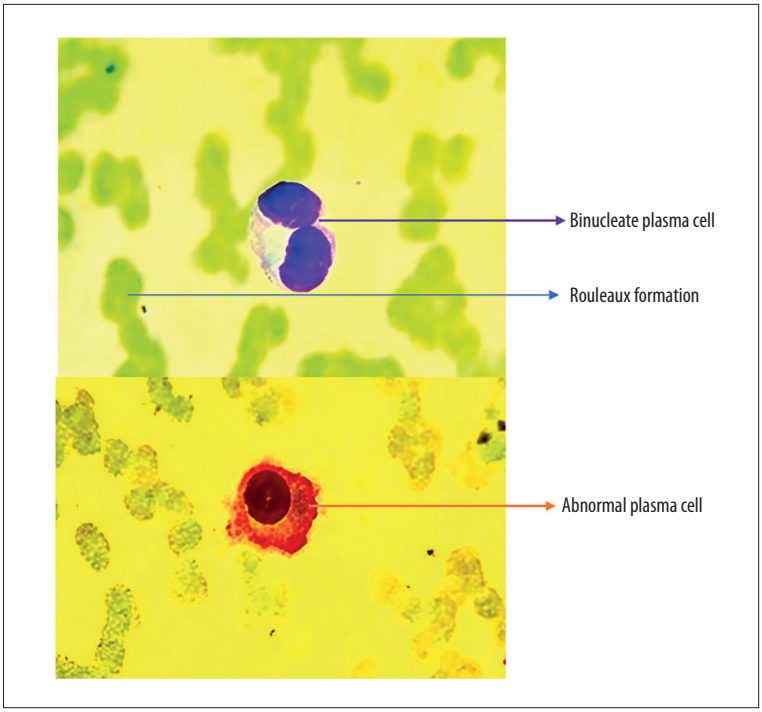

Figure 2. Bone marrow aspirate.
Top panel: Abnormal plasma cell with binucleation and rouleaux formation of erythrocytes in the background.
Bottom panel: Abnormal plasma cell with eccentric nuclei.

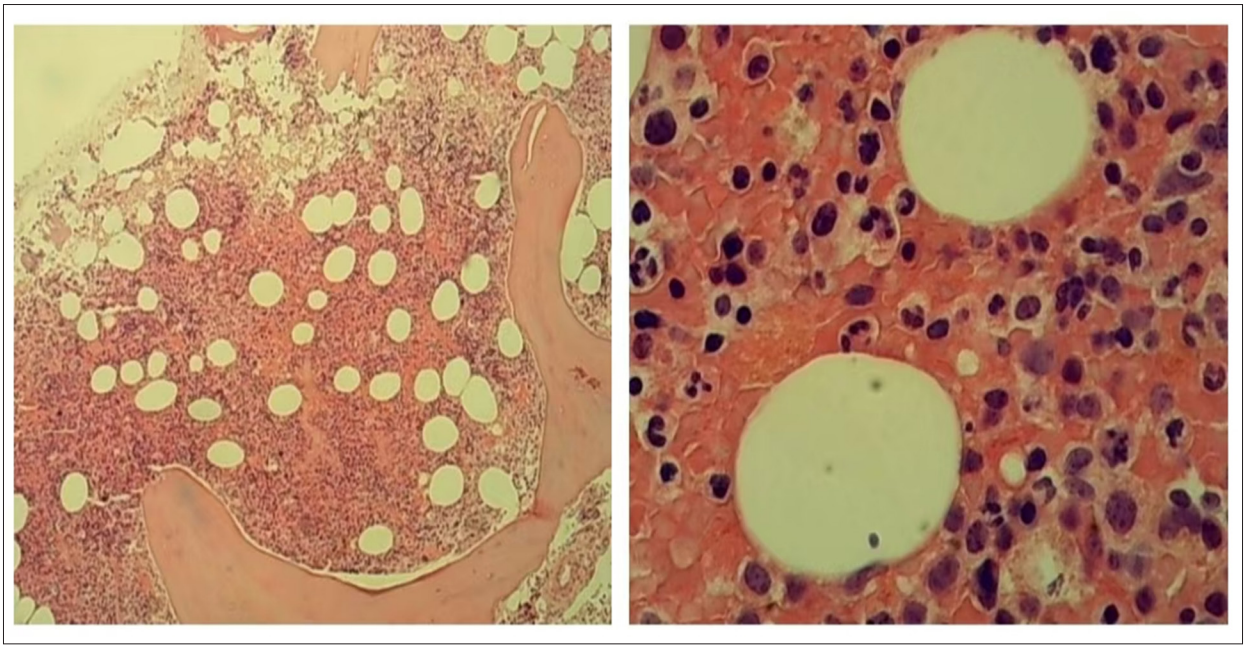

Figure 3. Bone marrow biopsy. Only 1 focal aggregate contained more than 15 mast cells and no multifocal dense aggregates.

Serum protein electrophoresis revealed the following levels: immunoglobulin M, 0.41 g/L; immunoglobulin G, 34.9 g/L; light chain λ, 8.45 g/L; light chain κ, 43.10 g/L. Immunofixation revealed the presence of a monoclonal IgG-λ paraprotein. In addition, compared with the data from 3 years ago, the patient presented with renal function impairment (creatinine level 144.4 μmol/L, glomerular filtration rate 31.0 ml/min, β-2 microglobulin 6.87 mg/L) (**Table 2**). Repeat BMA revealed myeloid blasts accounting for 3%, decreased band neutrophils, easily observed neutrophils with bilobed nuclei, increased numbers of plasma cells accounting for 10.5%, naive and binucleate plasma cells occasionally observed (**Figure 2**), active erythropoiesis with rouleaux formation, and a total of 39 megakaryocytes were found. Bone marrow biopsy (BMB) showed that mast cells were scattered in the bone marrow cavity, with only one focal aggregate containing more than 15 mast cells and no

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Table 3. Comparison of the patient's features to the SM diagnostic criteria. WHO diagnostic criteria for SM: if a diagnosis of SM is made, at least 1 major and 1 minor or 3 minor criteria should be fulfilled.

Diagnostic criteria	Systemic mastocytosis (SM)	Patient
Major criterion	≥15 mast cells in multifocal dense infiltrates in bone marrow biopsies and/or in sections of other extracutaneous organs	A single mast cell aggregate with >15 cells in bone marrow biopsies
Minor criteria	(1) ≥25% of all mast cells are spindle-shaped	(1) 10% oval-shaped mast cells
	(2) KIT-activating at codon 816 or in other critical regions	(2) KIT D816V mutation negative. Other KIT mutations were not tested
	(3) Mast cells express one or more of: CD2 and/or CD25 and/or CD30	(3) CD117 positive, CD2 and CD30 negative. CD25 was not tested
	(4) Baseline serum tryptase concentration >20 ng/mL	(4) Baseline serum tryptase concentration 19.1 ng/mL

The diagnosis of SM requires meeting either the major criterion and at least 1 minor criterion, or at least 3 minor criteria concurrently.

multifocal dense aggregates (**Figure 3**). Immunohistochemistry (IHC) revealed 10% round mast cells with positive expression of CD117 and negative expression of CD2 and CD30 (CD25 was not performed), and 10.5% myeloma cells with positive expression of CD138 and Lambda and negative expression of Kappa. The flow cytometry indicated that a cluster of abnormal plasma cells accounted for 1.72%, with positivity for CD38, CD138, and CD56. Furthermore, a cluster of myeloid blasts accounted for 0.18%, with positive for CD38, CD13, and CD45, and reduced expression of CD33. The total serum mast cell tryptase concentration was 19.1 (0.0-20.0) ng/ml, and the C-KIT (Exon17) mutation was negative using Sanger sequencing, with an analytical sensitivity of 10%. No further sequencing of the KIT gene was performed. In addition, the patient did not exhibit any SM-related B findings (such as mast cells over 30%) or C findings (such as organ damage) [11]. Cytogenetic testing revealed 47, XX +8[17]/46, XX [3]. Chest computed tomography revealed a mosaic pattern of the bilateral lungs and coronary arteriosclerosis. A Doppler echocardiogram revealed a thickened mitral valve, mild tricuspid regurgitation, a normal left ventricular ejection fraction (EF) of 61%, and slightly decreased left ventricular diastolic function. The electrocardiogram (ECG) was normal.

According to the diagnostic criteria of SM [11] (**Table 3**), only a single mast cell aggregate with >15 cells in the BMB was found in this patient, which did not meet the major diagnostic criteria. The results, including CD117 positive, CD2 and CD30 negative, and a baseline serum tryptase level of less than 20 ng/ml, did not meet any of the minor criteria. It is a pity that CD25 and comprehensive KIT gene sequencing were not performed for this patient due to poor compliance. As a result, she was finally diagnosed with active MM (IgG λ-type, DS stage II, ISS stage III) accompanied by mast cell hyperplasia and low-level myeloid blastocytosis.

Treatment and Outcome

Based on the diagnosis of mast cell hyperplasia and the low-level myeloid blastocytosis, we decided to monitor only these 2 populations without intervening. The re-evaluation demonstrated an increase in both plasma cells and M-protein compared to the results 3 years ago, accompanied by pancytopenia and renal impairment (**Table 1**). These findings confirmed the progression from MGUS to active MM. Although the patient had a history of RA, relevant laboratory results were within normal range, and she lacked typical clinical features such as joint deformity or pain. Furthermore, she had no long history of medication taking, thus excluding RA and drug-induced renal impairment. Although a renal biopsy had not been performed, it is reasonable to infer that the renal impairment was attributable to plasma disease progression. Owing to the patient's severe pancytopenia, advanced age, comorbidities, and Eastern Cooperative Oncology Group (ECOG) score of 2, a treatment regimen of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11) combined with dexamethasone (20 mg on days 1, 4, 8, and 11) was given. We monitored the results of routine blood tests, and the necessary transfusion of blood components was provided regularly. After 1 cycle of treatment, the patient was admitted to the ward with slightly lower IgG-λ quantification than before. There was no significant improvement in her blood cell recovery or kidney function. To reduce the frequency of admission, an oral regimen of isatuximab (4 mg on days 1, 8, and 15) combined with dexamethasone (20 mg on days 1, 8, and 15) was given. Unfortunately, 3 weeks after discharge, the patient experienced an acute myocardial infarction and died in the emergency clinic.

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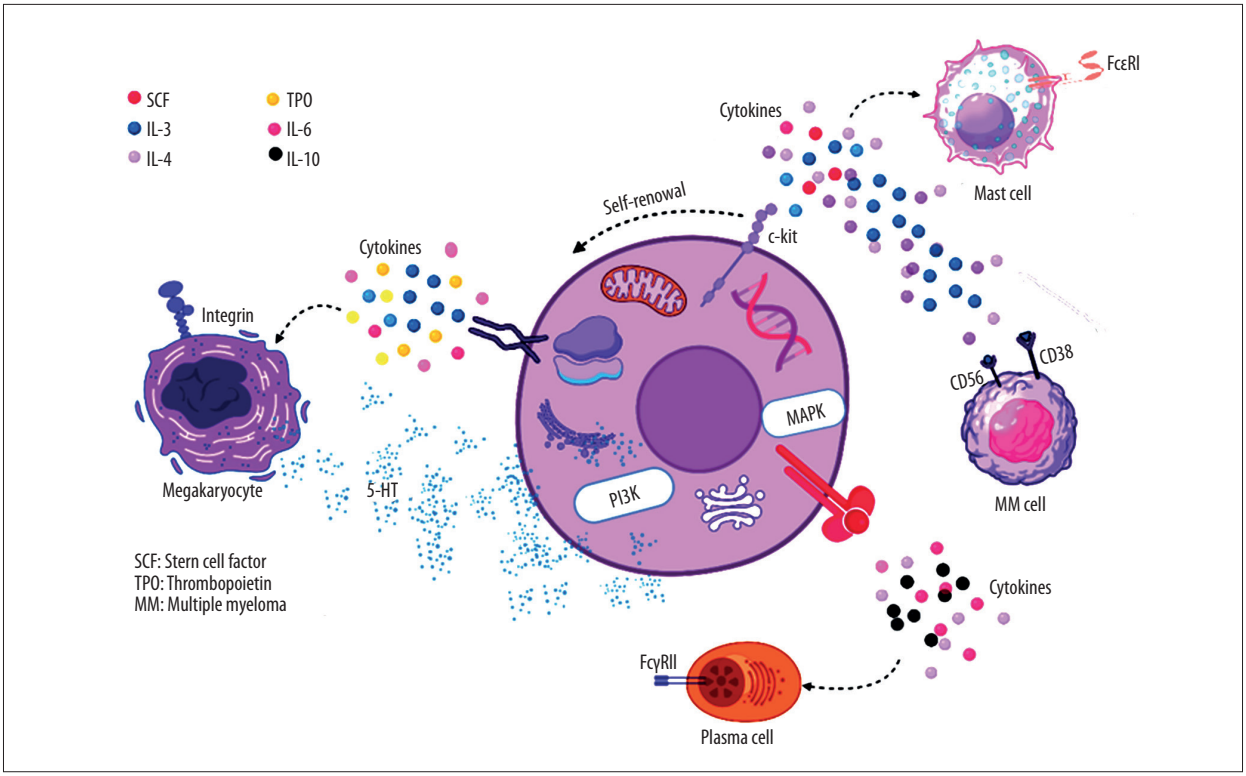

Figure 4. The ontogeny of hematopoietic stem cells (HSCs). All hematopoietic cells originate from HSCs. HSCs give rise to diverse blood cell types through lineage-specific differentiation. For instance, SCF supports the development of multipotent hematopoietic progenitors, whereas TPO specifically regulates megakaryocytic lineage differentiation, demonstrating the multipotency of HSCs. Moreover, cytokines act directly on HSCs to maintain the self-renewal to increase their number.

Discussion

We report a rare case of a patient with mast cell hyperplasia, low-level myeloid blastocytosis, and a long history of plasma cell disorders. She was initially diagnosed with MGUS with no significant mast cells in the bone marrow. During the 3-year follow-up, she gradually developed pancytopenia. BMA confirmed that the percentage of monoclonal myeloma cells increased to 10.5%. Additionally, there were 2 clusters of low-level myeloid blastocytosis (0.18%) and mast cells (10%) in the bone marrow. The low-level myeloid blastocytosis in this patient was a minor finding: 0.18% by flow cytometry and 3% in BMA, which did not meet diagnostic criteria for acute myeloid leukemia (AML) or classical myelodysplastic syndrome (MDS), and thus could not be regarded as a separate neoplasm. Although she received 2 cycles of a proteasome inhibitor combined with dexamethasone, there was no significant improvement in her laboratory test indicators or clinical manifestations.

Initially, we thought that this case should be classified as SM-AHN, as it is most frequently found with myeloid malignancies, and hematological neoplasms can be diagnosed before, after, or simultaneously with SM [12]. As mentioned above, SM could not be excluded due to the 10% analytical sensitivity of Sanger sequencing and the lack of CD25 detection and broader KIT gene testing. However, normal serum tryptase levels, negative results for the most common KIT D816V mutation, and IHC (positive CD117 and negative CD2 and CD30) supported the classification as reactive mast cell hyperplasia.

First, The causes of reactive mast cell hyperplasia include immunoglobulin E-associated disorders, connective tissue disorders, infectious diseases, neoplastic disorders, lymph nodes draining areas of tumor growth, osteoporosis, chronic liver disease, and chronic renal disease. The above diseases might induce persistent inflammatory stimulus and alter the microenvironment (such as an increase of SCF and IL-4), which finally induces a reactive increase of mast cells [8,9]. Inflammatory conditions such as arthritis and certain drugs are also potent stimuli for mast cells [1,13]. Until now, the association between MM and reactive mast cell hyperplasia has been unclear. There have been few reported cases of reactive mast cell hyperplasia to date [14], and only 1 case has been reported (Wu et al) in which the patient was diagnosed with acute basophilic leukemia accompanied by reactive mast cell hyperplasia [15]. In that case, flow cytometry results showed mast cells accounted for 1.15% of nuclear cells, expressing CD203c but not CD25 and CD2. Meanwhile, no mast cell infiltration was observed in

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bone marrow biopsy and other sites, and no obvious skin lesions were observed. Finally, the patient chose to be discharged due to worsening condition. For our patient, the coexistence of MM, mast cell hyperplasia, and low-level myeloid blastocytosis was confirmed. Owing to the small number of mast cells observed, we only administered therapeutic agents indicated for patients with MM. However, several aspects of this case could not be explained by the plasma disorders. We hypothesize that there might be several reasons for the coexistence of MM, mast cell hyperplasia, and low-level myeloid blastocytosis.severe pancytopenia could not be fully interpreted by MM because there were only 10.5% abnormal plasma cells, and the concentration of IgG-λ was not very high, indicating a lower tumor burden. Second, SM-AHN is most frequently found in patients with myeloid malignancies [7]. Our patient had a small colony of low-level myeloid blastocytosis. However, this colony was too small, and the c-KIT mutation and serum mast cell tryptase levels were normal. Therefore, we believed that it should not be classified as SM-AHN. Thirdly, our patient presented simultaneously with 3 clusters of abnormal cells during bone marrow examination: low-level myeloid blastocytosis (0.18%), plasma cells (10.5%), and mast cells (10%), suggesting a defect in multiple hematopoietic stem cells. These cells proliferate and differentiate into common myeloid progenitors and common lymphoid progenitors (**Figure 4**). Mast cells and myeloid blasts are derived from the former, and plasma cells were derived from the latter. Although the patient could not be diagnosed with myeloid neoplasms, including MDS, abnormalities at the level of myeloid progenitors could not be excluded.

The reactive proliferation of mast cells can be driven by cytokines that promote their growth and differentiation. The interaction between myeloma cells and the bone marrow microenvironment mediates the production of adhesion molecules that increase tumor growth and survival, resulting in the secretion of cytokines and growth factors, including interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), the tumor necrosis factor superfamily (TNFSF), and interleukin 10 (IL-10) [16]. In addition to the most significant stem cell factor (SCF), which is the ligand for the tyrosine kinase receptor KIT and can induce mast cell proliferation, other common factors, such as IL-3, IL-4, and IL-6, also possess this capability [1,17]. Ghanem et al reported the case of a patient with ISM who was found to have concomitant smoldering multiple myeloma (SMM) that eventually progressed to active MM (aMM) [18]. Lakritz et al, Ramya et al, and Preetesh et al also reported relevant cases of SM and MM [14,19,20]. Therefore, the aberrant secretion of MM might lead to the proliferation and differentiation of mast cells. Unfortunately, these cytokines were not evaluated in this patient.

There are some limitations to our report. It would have been ideal to search for more IHC biomarkers, especially CD25. Furthermore, the KIT D816V mutation is detected in over 90% of patients with SM, while most patients do not have other KIT mutations, such as KIT D816H/Y and N822K [21]. Due to the poor compliance and the death of our patient, we did not get authorization from her relatives to perform more IHC or molecular tests.

Conclusions

Here, we report a rare case of a patient diagnosed with multiple myeloma (MM), mast cell hyperplasia, and low-level myeloid blastocytosis. For the pancytopenia observed in this patient, MM was our primary consideration, despite a relatively low tumor burden (10.5% bone marrow plasma cells). Given the concurrent presence of mast cell hyperplasia and low-level myeloid blastocytosis in this case, we believe that the severe pancytopenia was most likely related to the combined abnormal proliferation of these 3 cell lineages. Hypothetically, the coexistence of these 3 hematopoietic abnormalities arises because (1) multiple abnormal hematopoietic stem cells differentiate into myeloid progenitors and lymphoid progenitors, resulting in pancytopenia, mast cell hyperplasia, and MM; or (2) the cytokines and growth factors secreted from MM promote the hyperplasia of mast cells.

Definitive classification of mast cell proliferation (SM or reactive mast cell hyperplasia) in patients requires comprehensive testing, including bone marrow biopsy for multifocal dense infiltrates, immunophenotyping for CD25, CD2, and CD30, and full KIT gene sequencing (not just KIT D816V). In our case, distinguishing reactive mast cell hyperplasia from SM would have been more reliable if CD25 testing and comprehensive KIT mutation analysis had been performed. More mechanistic evidence and similar cases are needed to better understand the complex multilineage dysplasia in one patient. Unlike SM, treatment choices for reactive mast cell hyperplasia are limited, and the most accepted approach is primary disease control. The clinical response for our patient was poor, indicating that it might be insufficient to treat such patients with only agents associated with MM. Due to the scarcity and poor outcomes of such patients, more similar reports are needed, and better treatment options are expected in the future.

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Patient Consent Declaration

Written informed consent was obtained from the patient's family for publication of this case report.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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