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Rare Case of Multiple Lineage Dysplasia Myelodysplastic Syndrome Presenting with Only Anemia: A Case Report

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Abstract

BACKGROUND: Myelodysplastic syndrome (MDS) is a heterogeneous group of hematopoietic stem cell disorders which is characterized by ineffective hematopoiesis and risk of progression into acute myeloid leukemia. The diagnosis and classification of MDS are determined from the findings of dysplasia in one or more cell lineage and the percentage of blast cell on bone marrow examination. However, it should be noted that an abnormality in one marrow cell lineage does not necessarily translate to the corresponding clinical phenotype. Here, we present a case of MDS with multilineage dysplasia (MLD) (erythrocyte, leukocyte, and thrombocyte) from bone marrow aspiration, but with anemia as the sole clinical manifestation (single cytopenia).

CASE REPORT: A 78-year-old male patient came to our clinic on July 10, 2020, with chief complaint of worsening fatigue which started approximately 1 year before visit. His vital signs during the visit were stable and no other abnormalities observed other than pale conjunctivae. Complete blood count showed macrocytic anemia with no abnormalities in leukocyte count and thrombocyte count, which suggested a single cytopenia. Peripheral blood smear was negative for megaloblasts and hypersegmented neutrophils. The patient's bone marrow examination showed MDS with MLD. This result was in contrast to complete blood count examination which only showed anemia (single cytopenia).

CONCLUSION: This case showed that there could be discrepancy between clinical manifestations of the cytopenia with bone marrow dysplasia, which highlighted the importance of conducting bone marrow examination to properly classify MDS type.

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematopoietic stem cell disorders which is characterized by ineffective hematopoiesis and risk of progression into acute myeloid leukemia [1], [2]. The ineffective hematopoiesis can occur in one or more cell types (red blood cells, white blood cells, and platelets) [2], [3], [4]. Interestingly, MDS has a wide range of clinical phenotypes with some patients remain asymptomatic while others express aggressive phenotype that quickly progress into refractory leukemia [2], [4], [5].

MDS has a tendency to occur in the elderly. Studies by Ma and Sekeres *et al*. reported age at presentation of 70 years or older [6], [7]. Furthermore, it is rarely diagnosed in people under 50 years old and is more common in males [8], [9].

The latest World Health Organization (WHO) classification of MDS was published in 2016 and served as a guideline for clinicians [10]. Here, classification of MDS is based from dysplasia in one or more cell lineage and percentage of blast cell on bone marrow examination [10]. However, it should be noted that an abnormality in one marrow cell lineage does not necessarily translate to the corresponding clinical phenotype [11], [12]. Here, we present a case of MDS with multilineage dysplasia (MLD) (erythrocyte, leukocyte, and thrombocyte) from bone marrow aspiration, but with anemia as the sole clinical manifestation (single cytopenia).

Case Presentation

A 78-year-old male patient came to our clinic on July 10, 2020, with chief complaint of worsening fatigue which started approximately 1 year before visit. No other complaints or symptoms were observed at that

time. A medical and familial history was insignificant. His diet was nutritionally adequate. There was also no significant history of exposure to toxic agents or chemotherapy. His vital signs during the visit were stable and no other abnormalities observed other than pale conjunctivae.

Table 1: Laboratory data on July 10, 2020

Parameter (units)	Result	Reference range, adults
Hemoglobin (g/dL)	7.9	13.2–17.3
Hematocrit (%)	22%	40–52%
Erythrocytes (×10^{12}/L)	2.01	4.4–5.9
Mean corpuscular volume (fL)	108	80–100
MCH (pg)	41	26–34
MCHC (g/dL)	38	32–36
Reticulocyte (%)	1.8	0.5–1.5
Corrected reticulocyte count (%)	0.99	0.5–1.5
Absolute reticulocyte count (×10^{6}/L)	36.1	20–75
WBC (×10^{9}/L)	5.1	4.5–11
Basophil (%)	1	0–1
Eosinophil (%)	3	2–4
Band neutrophil (%)	0	3–5
Segmented neutrophil (%)	68	50–70
Lymphocyte (%)	19	25–40
Monocyte (%)	9	2–8
Platelet (×10^{9}/L)	298	150–440
Bleeding time (minutes)	3	0–6
Prothrombin time (seconds)	10.6	9.3–11.4
Activated partial thromboplastin time (seconds)	31.7	11–47
Total protein (g/dL)	6.8	6.6–8.8
Albumin (g/dL)	3.8	3.5–5.2
Globulin (g/dL)	3	2.3–3.5
AST (U/L)	26	<35
ALT (U/L)	24	<41
Creatinine (mg/dL)	1.5	0.9–1.3
Estimated glomerular filtration rate* (ml/min/1.73 m^2)	44–51	-

*Based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

Complete blood count and iron studies were performed on July 10, 2020, and July 11, 2020, and the results are shown in Tables 1 and 2, respectively. Macrocytic anemia was observed based on the low hemoglobin level and increased mean corpuscular volume (MCV). Vitamin B12 level was observed to be elevated (2768 pg/mL). No abnormalities were observed in leukocyte count and thrombocyte count, which suggested a single cytopenia. The patient had slightly elevated creatinine. Furthermore, the liver function tests were normal. As a result, bone marrow examination was considered for additional examination to confirm the etiology of macrocytic anemia but the patient declined. The patient was then scheduled for packed red cell (PRC) transfusion to increase hemoglobin level.

Table 2: Iron studies and Vitamin B12 data on July 11, 2020

Parameter (units)	Result	Reference range, adults
Serum iron (mcg/dL)	152	65–175
Total iron-binding capacity (mcg/dL)	181	250–425
Ferritin (ng/mL)	395.77	21.81–274.66
Vitamin B12 (pg/mL)	2768	187–883

On September 4, 2020, the patient returned for a routine check-up and complete blood count was performed. The result showed some improving parameters: Hemoglobin level of 9.6 g/dL, hematocrit 26%, and RBC count 2.45 × 10^{12}/L. Peripheral blood smear showed anisocytosis and macrocytic anemia without the presence of megaloblasts and hypersegmented neutrophils. Ferritin level increased to 641.73 ng/ml. Additional examination such as the direct and indirect Coombs' tests was negative. Stool examination showed no sign of occult bleeding as well as infections or parasitic infestation. The patient was then advised again to take bone marrow aspiration examination.

Bone marrow aspiration was conducted on February 22, 2021 (Table 3). Morphological assessment of bone marrow revealed normal cellularity. Other findings included increased erythropoiesis with dyserythropoiesis and increased granulopoiesis with shift to left. Blast cell percentage was within normal limit (0.5%). Thrombopoiesis was decreased with signs of dysmegakaryopoiesis. Based on the marrow morphological examinations, a diagnosis of MDS with MLD was established.

Table 3: Bone marrow examination on February 22, 2021

Parameter (units)	Result	Reference range, adults
Marrow cellularity	Normal	Normal
Marrow adipose tissue	Normal	Normal
Blast (%)	0.5	0.1–1.1
Progranulocyte (%)	1	-
Myelocyte (%)	14	2.6–13.5
Metamyelocyte (%)	6.5	5–20.8
Band neutrophil (%)	4.5	10.8–20.4
Segmented neutrophil (%)	23.5	7–37.8
Basophil (%)	1	0–0.6
Eosinophil (%)	1	0.4–4.4
Rubriblast (%)	1	0–1
Prorubriblast (%)	3	0.1–3.2
Rubricyte (%)	10.5	4.2–12.8
Metarubricyte (%)	17.5	6.6–33.4
Total myeloid (%)	51	-
Total erythroid (%)	32	-
Myeloid-erythroid ratio	1.6:1	-
Megakaryocyte count	Increased	Normal
Abnormal morphology	Dysthrombopoiesis observed	-
Thrombocyte formation	Reduced	-

Immunophenotyping from the bone marrow showed no dominant immunophenotype marker. Cytogenetic examination showed nonrandom karyotype abnormalities of chromosome 7 deletion, trisomy 13, and trisomy 22 which correspond to poor prognosis based on cytogenetic risk group from revised international prognostic scoring system (IPSS-R) cytogenetic risk group [13].

The patient was then treated with lenalidomide to increase hemoglobin and induce transfusion independence. However, no response was observed after a few months of therapy and subsequently, treatment was switched to erythropoietin (EPO) supplementation which also showed no response. The patient was subsequently given supportive treatment and periodic transfusions.

Discussion

MDSs are clonal hematopoietic disorders which have variable clinical course and prognosis [4], [14]. The symptoms of MDS are often related to the chronic unexplained cytopenia. For example, MDS patients may have symptoms of fatigue caused by anemia, bleeding if thrombocytopenic, and infection in leukopenia [14]. Anemia is the most common cytopenia in MDS, however, many patients can be asymptomatic,

especially in early stage MDS [15]. Therefore, the diagnosis of MDS can be challenging for clinicians due to lack of specific symptoms.

Diagnosis of MDS presenting with anemia

For patients presenting with anemia, a careful previous medical history and physical examination must be obtained to exclude possible causes of iron deficient anemia, anemia of chronic disease, and hemolytic anemia. Routine laboratory examinations consisting of complete blood count, iron studies, reticulocyte count, peripheral blood smear, and Vitamin B9/B12 must also be conducted to exclude common causes of anemia [2], [4], [5]. History of toxic exposure to benzene, chemotherapy, and pesticides should be checked since these can increase risk of MDS. Thus, other possible causes of anemia should be excluded first before clinical suspicion of MDS is made.

The anemia in MDS is often macrocytic, although occasionally it may also present as normocytic anemia [15], [16], [17]. The MCV in this patient was elevated which suggested macrocytic anemia. In our case, the peripheral blood smear was negative for megaloblasts and hypersegmented neutrophils, which supported the diagnosis of non-megaloblastic anemia. Further supporting the non-megaloblastic anemia was the elevated Vitamin B12 level in this patient. Several causes of non-megaloblastic anemia are alcohol abuse, liver disease, MDS, and congenital bone marrow failure syndromes [18]. In this patient, there was no history of alcohol abuse and the symptoms of anemia never occurred previously. In addition, the liver function tests were normal. Finally, the corrected reticulocyte count was normal, suggesting a pathological process in bone marrow. Thus, MDS remained as a possible cause of the macrocytic non-megaloblastic anemia in this patient.

The patient's bone marrow examination showed MDS with MLD. This result was in contrast to complete blood count examination which only showed anemia (single cytopenia). The findings of dysgranulopoiesis and dysthrombopoiesis from the bone marrow did not manifest as leukopenia and thrombocytopenia. Therefore, this case showed that there could be discrepancy between clinical manifestations of the cytopenia with bone marrow dysplasia, which highlighted the importance of conducting bone marrow examination to properly classify MDS type.

Ferritin in MDS

Patients with MDS often have elevated serum ferritin due to periodic transfusion [19]. Nonetheless, elevated serum ferritin can also be observed in MDS patients before transfusion which may occur due to ineffective erythropoiesis resulting in unused iron [20], [21]. Hence, serum ferritin may be useful to help diagnosing MDS since elevated serum ferritin in anemia could suggest the presence of dyserythropoiesis which may be attributed to bone marrow abnormalities. A recent study by Kikuchi *et al*. showed that serum ferritin level at diagnosis correlated with survival time and leukemia-free survival for MDS [22].

Role of cytogenetic in MDS

Cytogenetic examination of the bone marrow is an important diagnostic modality in MDS as evidenced by its incorporation in the WHO classification for risk stratification [10]. The study by Haase *et al*. with sample size of 2124 MDS patients showed that more than 50% of patients had cytogenetic abnormalities using standard karyotyping [23]. However, standard karyotyping technique has a limitation of being unable to detect cryptic chromosomal aberrations such as microdeletions and copy number neutral loss of heterozygosity. On the other hand, new techniques for cytogenetic analysis consisting of fluorescence *in situ* hybridization and single-nucleotide polymorphism arrays revealed that cryptic chromosomal aberrations can be observed in some MDS patients [24], [25].

It is interesting to note that in contrast to other hematological cancers where chromosomal translocations and inversions are dominant, MDS has higher number of chromosomal deletions and duplications [26]. There are many frequent cytogenetic abnormalities observed in MDS such as del(5q), del(20q), trisomy 8, and monosomy 7 [24], [26], [27].

MDS with del(5q) presents such important prognostic value that in the latest WHO guideline, it is classified as a unique type MDS due to high response rate to lenalidomide therapy [2], [10], [28]. Around 30% of MDS cases have del(5q), which also means that only around up to 30% of MDS patients theoretically have good response to lenalidomide [23], [28], [29]. The reason for this phenomenon is mainly caused by haploinsufficiency of multiple genes due to deletion in chromosome 5 region, in particular, haploinsufficiency of casein kinase 1 alpha 1 (CSNK1A1) gene which produces casein kinase 1A1 [30], [31]. Due to haploinsufficiency of CSNK1AI resulting in decreased expression of casein kinase, the cells become vulnerable to further reduction in casein kinase expression, which can be induced by lenalidomide through degradation of CSNK1AI through ubiquitination [32]. Hence, normal hematopoiesis is restored by suppression of clonal cells with del(5q). In contrast, normal cells with two copies of CSNK1A1 can tolerate the degradation of CSNK1AI by lenalidomide due to higher amount of CSNK1AI.

The cytogenetic abnormality of del(20q) is associated with good prognosis in MDSs [13]. The reasons for this come from observation that *de novo* MDS patients with isolated del(20q) have a tendency for indolent clinical course [33], [34]. However, the patients often have thrombocytopenia [35].

Monosomy of chromosome 7 indicates a poor prognosis [13], [36]. On the other hand, isolated del(7q) confers better prognosis [37]. The exact pathophysiology on how monosomy of chromosome 7 confers a poor prognosis is still incompletely understood but it is suspected that genes in chromosome 7 such as MLL3 may play a role [37], [38]. Other cytogenetic abnormalities are also observed in MDS but their significance is still unknown.

Role of revised international prognostic scoring system for MDSs

The WHO classification for MDS does not confer prognosis information which limits its utility in clinical setting. At present, one of the widely used scoring systems for MDS to determine prognosis is IPSS-R, introduced in the year 2012 [13]. The scoring system by IPSS-R uses cytogenetics, bone marrow blast, hemoglobin, platelets, and absolute neutrophil count. However, it should be noted that the estimated medical survival times in IPSS-R are based on untreated MDS patients [13]. Hence, the median survival times for treated MDS patients, irrespective of the prognosis based on IPSS-R may be longer. The main limitation of IPSS-R is lack of comorbidities incorporation for the prognosis, especially since MDS is a disease of the elderly that tend to have multiple comorbidities. Additional limitation is that the scoring system does not include serum ferritin and lactate dehydrogenase for prognosis of MDS patients despite several studies have shown the prognostic role for both of these variables [22], [39], [40].

In the case presented here, the patient showed multiple karyotype abnormalities involving chromosome 7 deletion, trisomy 13, and trisomy 22, which according to IPSS-R, this patient was grouped into poor prognostic subgroup on the MDS cytogenetic scoring system [13]. The cytogenetic subgroup's result was then combined with the laboratory data, resulting IPSS score of 4.5 which correspond to a high-risk category.

Selecting treatment for MDS

The choice of MDS treatment is determined mostly by risk stratification from IPSS-R, with higher-risk MDS given more aggressive active treatment than patients with lower-risk MDS [2]. However, prognostic risk should not be the sole factor to determine treatments. For example, caution should be exercised in elderly patient with higher-risk MDS when considering hypomethylating agents or chemotherapy as treatments. Benefits and risks must be weighted and discussed with the patient. Another example is consideration to provide stem cell transplantation in young patients with lower-risk MDS with the purpose to achieve highest survival possible.

Anemia management in MDS

There are three main treatment modalities that can be used for anemia: (1) Periodic PRC transfusion, (2) periodic erythropoiesis-stimulating agents (ESAs) injections, and (3) lenalidomide [2], [4].

Routine use of PRC transfusion can alleviate the symptoms of anemia, especially in patients with hemoglobin below 8 mg/dL [41], [42]. However, some patients such as older MDS patients may receive benefit from more liberal threshold as shown in an exploratory clinical trial by Stanworth *et al*. [42]. In the study, quality of life was significantly improved in the liberal group (10.5 mg/dL) when compared with the restrictive group (8 mg/dL). Nevertheless, routine transfusion is not recommended and should be avoided if possible due to the associated risks from transfusion such as iron accumulation, infection, and transfusion reactions. As a matter of fact, routine transfusion is a predictor for worse outcome in MDS [43].

A strategy to reduce transfusion dependence is using ESAs. Many studies have shown that a significant percentage of patients responded to ESAs supplementation and achieved hemoglobin improvement [4], [44], [45], [46]. One of the predictors for ESAs response is pre-treatment serum EPO levels of <500 U/L [47]. Hence, pre-treatment EPO should be measured to determine MDS patients that can benefit from ESAs. However, use of ESAs can also be considered in patients with EPO of ≥500 U/L as some patients may still respond to the treatment [2], [44], [47].

Lenalidomide can also be used to achieve transfusion independence, however, as stated above, the predictor for lenalidomide response is presence of del(5q) [28], [32]. If given to population of MDS patients without del(5q), only around 26.9% of patients achieved transfusion independence [48]. Furthermore, the response is usually short-lived.

In our patient, lenalidomide was given despite the patient not having del(5q). The reason for this was the old age of the patient where periodic transfusion should be avoided if possible. Furthermore, despite being higher-risk MDS, we did not give intensive chemotherapy or hypomethylating agents due to side effects which might be detrimental for the patient such as infection.

After treatment with lenalidomide, no improvement was observed. The patient was then given ESAs supplementation but similarly, no response was observed. Unfortunately, we did not measure pre-treatment serum EPO level before ESAs, hence, whether the ESAs failure was due to already elevated serum EPO or other causes could not be determined.

Conclusion

Diagnosing MDS is very challenging and requires comprehensive clinical and laboratory assessment. Bone marrow examination plays an important role in determining lineage dysplasia as clinical cytopenia does not always come in line. Cytogenetic analysis helps in determining prognosis of MDS patients. Treatments for anemia in MDS consisted of periodic PRC transfusion, periodic ESAs injections, and lenalidomide.

Statement of Ethics

Oral informed consent was obtained from the patient for publication of this case report.

Authors' Contributions

IR and NS were the physicians who treated the patient in this report. LS and ASK provided cytogenetic interpretation of the patient. The manuscript was prepared by IR, NS, KW, and LS. All authors participated in discussions about the manuscript and approved the final version.

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