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Role of bone marrow examination in distinguishing megaloblastic anemia from myelodysplastic syndrome

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Abstract:
Megaloblastic anemia and myelodysplastic syndrome can present with overlapping macrocytic anemia and cytopenias but require distinct management. Therefore, it is of interest to evaluate the diagnostic utility of bone marrow examination in 120 patients, comprising 70 with megaloblastic anemia and 50 with myelodysplastic syndrome, using clinical, hematological, biochemical and marrow findings. Megaloblastic anemia accounted for 58.3% of cases, while myelodysplastic syndrome accounted for 41.7%; patients with myelodysplastic syndrome were significantly older (63.4 ± 10.8 vs. 41.8 ± 12.6 years; $p<0.001$). Megaloblastic maturation, erythroid hyperplasia and giant metamyelocytes predominated in megaloblastic anemia, whereas dysgranulopoiesis, dysmegakaryopoiesis, ring sideroblasts and increased blasts characterized myelodysplastic syndrome. Bone marrow morphology integrated with clinical and biochemical findings enable reliable differentiation of these disorders, supporting accurate diagnosis and appropriate treatment selection in patients with macrocytic anemia and cytopenias.

Keywords: Megaloblastic anemia (MA), myelodysplastic syndrome (MDS), bone marrow examination, macrocytic anemia, cytopenia, dysplasia, bone marrow morphology

Background:
The most important hematological disorders that present with macrocytic anemia, cytopenias and abnormal bone marrow morphology include megaloblastic anemia (MA) and myelodysplastic syndrome (MDS). Although different in pathogenesis and prognosis, both disorders often have overlapping clinical, hematological and morphological characteristics that can lead to difficulties in diagnosis **[1]**. It is important to differentiate these entities accurately as their treatment, disease course and outcomes are vastly different. The main causes of megaloblastic anemia are deficiency of vitamin B12, folate deficiency or failure of DNA synthesis. Failure of DNA synthesis causes impaired hematopoiesis, which causes anemia, leukopenia, thrombocytopenia or pancytopenia **[2]**. The classic symptoms of vitamin B12 deficiency are fatigue, weakness, glossitis and neurologic symptoms. Peripheral blood analysis usually shows macrocytosis, hyper segmented neutrophils and various levels of cytopenia **[3]**. The myelodys plastic syndromes are a group of clonal hematozootic stem cell disorders that involve ineffective hematopoiesis, peripheral blood cytopenias, dysplastic bone marrow abnormalities and a high risk for progression to AML. MDC is more common with age and affects mainly older patients. Common symptoms are fatigue, recurrent infections and bleeding abnormalities from cytopenias **[4]**. The diagnostic dilemma is the fact that severe megaloblastic anemias can cause marked dysplasia in the bone marrow that mimics MDS. Nuclear irregularities, multinuclearity and asynchronous maturation of erythroid precursors can be observed. Giant metamyelocytes and bizarre nuclear segmentation of granulocytic precursors may be seen. These features may simulate marrow dysplasia and result in misclassification if full evaluation is not done **[5]**. In most patients, morphological assessment is used in combination with clinical observations and laboratory parameters to assist in accurate diagnosis. Current diagnostic approaches continue to regard bone marrow examination as central to MDS diagnosis, particularly for assessment of dysplasia, blast percentage and exclusion of other causes of cytopenia **[6]**. The development of cytogenetics, flow cytometry and molecular diagnosis tools have helped to enhance the accuracy of the diagnosis of MDS. These investigations may not be easily accessible, however, especially in resource constrained environments **[7]**. Therefore, careful bone marrow examination remains a useful and essential tool for diagnosis. Prajapati *et al.* similarly emphasized the complementary diagnostic value of bone marrow aspiration and trephine biopsy, particularly when integrated with peripheral smear and biochemical investigations **[8].** There have been several studies emphasizing the need to identify the reversible causes of marrow dysplasia (vitamin B12 and folate deficiency) from clonal disorders such as MDS **[9]**. The diagnosis of megaloblastic anemia may lead to an unnecessary invasive investigation, inappropriate therapy, or delayed correction of nutritional deficiencies **[10–12]**. Therefore, it is of interest to assess the value of bone marrow examination in the differentiation of megaloblastic anemia from myelodysplastic syndrome with the aim of determining the diagnostic role of these two entities as anemia is a very common presentation of these disorders and the diagnostic accuracy is of concern.

Materials and Methodology:
Study design:
A prospective, observational, comparative study.

Study setting:
The study was carried out in Department of Pathology with the Department of Hematology of a tertiary level teaching hospital.

Study duration:
September 2023 to August 2025.

Sample size:
There were 120 patients enrolled in the study.

Study population:
Patients with macrocytic anemia, bicytopenia, pancytopenia and unexplained cytopenias who had bone marrow examination were selected.

Study groups:
Group A: Megaloblastic anemia (n = 70)

Group B: Myelodysplastic syndrome (n = 50)

Inclusion criteria:
[1] Patients 18 years of age and older.
[2] Patients with macrocytic anemia (MCV >100 fL).
[3] Patients who have unexplained cytopenias.
[4] Individuals having bone marrow aspiration and biopsy.
[5] Patients who are willing to give informed consent.

Exclusion criteria:
[1] Previously diagnosed leukemia.
[2] Aplastic anemia.
[3] Hematological malignancies other than MDS.
[4] Patients receiving chemotherapy.
[5] Patients with inadequate bone marrow samples.
[6] Patients refusing consent.

Clinical evaluation:
A thorough clinical history was obtained, including the age, gender, onset and severity of the symptoms, dietary habits and medications, alcohol and drug use and any other medical conditions. Physical examination of pallor, hepatomegaly, splenomegaly, lymphadenopathy, glossitis and neurological manifestations.

Laboratory investigations:
The following investigations were carried out:
[1] Complete blood count (CBC) analysis by automated hematology analyzer.
[2] Examination of peripheral blood smear
[3] Reticulocyte count.
[4] Estimation of vitamin B12 in serum.
[5] Serum folate levels.
[6] Serum lactate dehydrogenase.
[7] Liver function tests.
[8] Renal function tests.

Bone marrow examination:
The posterior superior iliac spine was used for bone marrow aspiration with strict aseptics. The smears were stained with Leishman stain and were examined under the microscope. Bone marrow biopsy was performed and stained with hematoxylin and eosin. The following parameters were tested:
[1] Marrow cellularity.
[2] Myeloid-to-erythroid ratio.
[3] Erythroid hyperplasia.
[4] Megaloblastic maturation.
[5] Nuclear-cytoplasmic asynchrony.
[6] Giant metamyelocytes.
[7] Dysgranulopoiesis.
[8] Dysmegakaryopoiesis.
[9] Ring sideroblasts.
[10] Blast percentage.
[11] Marrow fibrosis.

Diagnostic criteria:
The diagnosis of megaloblastic anemia was made by characteristic marrow morphology and deficiency of either vitamin B12 or folate. Myelodysplastic syndrome was diagnosed based on the current World Health Organization/International Consensus Classification criteria which include morphology, cytopenias and blast count and ancillary investigations as available.

Statistical analysis:
All data were entered into the MS Excel and analyzed with IBM SPSS Statistics Version 29.0. Data of continuous variables were presented as mean ± SD and categorical variables frequencies and percentages. Chi-square test or Fisher's exact test was used for categorical variables. Continuous variables were analyzed using independent t-test. A p-value of <0.05 was deemed to be statistically significant.

Results:
A total of 120 patients presenting with macrocytic anemia, bicytopenia, pancytopenia, or unexplained cytopenia underwent detailed hematological evaluation and bone marrow examination. Based on clinical, biochemical and marrow findings, 70 patients (58.3%) were diagnosed with megaloblastic anemia (MA), while 50 patients (41.7%) were diagnosed with myelodysplastic syndrome (MDS). The mean age of patients with MDS was significantly higher than those with megaloblastic anemia (63.4 vs. 41.8 years, $p<0.001$). Male predominance was observed in both groups without statistical significance. Fever and bleeding manifestations were significantly more common in MDS patients, reflecting marrow failure and neutropenia. Neurological symptoms were significantly associated with megaloblastic anemia owing to vitamin B12 deficiency (30.0% vs. 4.0%; $p<0.001$) **(Table 1).** Patients with megaloblastic anemia showed significantly lower hemoglobin levels and greater macrocytosis than patients with MDS. Mean corpuscular volume was markedly elevated in MA (112.6 fL) compared with MDS (105.8 fL). Vitamin B12 deficiency was identified in 80% of MA patients compared with only 8% of MDS cases. Elevated LDH levels were significantly more frequent in MA because of ineffective erythropoiesis and intramedullary hemolysis **(Table 2).** Bone marrow morphology demonstrated marked differences between the two groups. Megaloblastic maturation, nuclear-cytoplasmic asynchrony, erythroid hyperplasia and giant metamyelocytes were significantly more frequent in megaloblastic anemia. Conversely, dysgranulopoiesis, dysmegakaryopoiesis, ring sideroblasts and increased blasts were significantly associated with MDS. These findings highlight the diagnostic value of marrow morphology in distinguishing the two disorders **(Table 3).** Megaloblastic maturation emerged as the most reliable marrow feature for diagnosing megaloblastic anemia, showing a sensitivity of 91.4% and specificity of 84.0%. Giant metamyelocytes also showed high diagnostic performance. Although erythroid hyperplasia was highly sensitive, its specificity was relatively low because a proportion of MDS patients also showed erythroid proliferation **(Table 4).**

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Table 1: Demographic and clinical characteristics of study participants

Variable	Megaloblastic Anemia (n=70)	Myelodysplastic Syndrome (n=50)	Total (n=120)	p-value
Mean Age (years)	41.8 ± 12.6	63.4 ± 10.8	50.8 ± 15.8	<0.001*
Male	40 (57.1%)	31 (62.0%)	71 (59.2%)	0.591
Female	30 (42.9%)	19 (38.0%)	49 (40.8%)	
Pallor	68 (97.1%)	46 (92.0%)	114 (95.0%)	0.217
Fatigue/Weakness	63 (90.0%)	42 (84.0%)	105 (87.5%)	0.328
Fever	15 (21.4%)	19 (38.0%)	34 (28.3%)	0.047*
Bleeding Manifestations	8 (11.4%)	16 (32.0%)	24 (20.0%)	0.006*
Splenomegaly	12 (17.1%)	14 (28.0%)	26 (21.7%)	0.154
Neurological Symptoms	21 (30.0%)	2 (4.0%)	23 (19.2%)	<0.001*

**Statistically significant*

Table 2: Comparison of hematological parameters

Parameter	Megaloblastic Anemia (n=70)	Myelodysplastic Syndrome (n=50)	p-value
Hemoglobin (g/dL)	7.4 ± 1.5	8.2 ± 1.8	0.008*
Total Leukocyte Count (×109/L)	3.1 ± 1.2	3.8 ± 1.4	0.004*
Platelet Count (×109/L)	88.4 ± 30.6	102.8 ± 35.4	0.018*
Mean Corpuscular Volume (fL)	112.6 ± 10.4	105.8 ± 9.6	<0.001*
Reticulocyte Count (%)	0.7 ± 0.3	1.2 ± 0.4	<0.001*
Serum Vitamin B12 Deficiency	56 (80.0%)	4 (8.0%)	<0.001*
Serum Folate Deficiency	28 (40.0%)	3 (6.0%)	<0.001*
Elevated LDH	62 (88.6%)	21 (42.0%)	<0.001*

**Statistically significant*

Table 3: Bone marrow morphological findings

Bone Marrow Feature	Megaloblastic Anemia (n=70)	Myelodysplastic Syndrome (n=50)	p-value
Hypercellular Marrow	62 (88.6%)	44 (88.0%)	0.917
Erythroid Hyperplasia	66 (94.3%)	29 (58.0%)	<0.001*
Megaloblastic Maturation	64 (91.4%)	8 (16.0%)	<0.001*
Nuclear-Cytoplasmic Asynchrony	61 (87.1%)	14 (28.0%)	<0.001*
Giant Metamyelocytes	55 (78.6%)	9 (18.0%)	<0.001*
Dysgranulopoiesis	12 (17.1%)	36 (72.0%)	<0.001*
Dysmegakaryopoiesis	6 (8.6%)	33 (66.0%)	<0.001*
Ring Sideroblasts	2 (2.9%)	17 (34.0%)	<0.001*
Increased Blasts (>5%)	0 (0%)	12 (24.0%)	<0.001*

**Statistically significant*

Table 4: Diagnostic utility of key bone marrow features in identifying megaloblastic anemia

Marrow Feature	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Megaloblastic Maturation	91.4	84.0	88.9	87.5
Nuclear-Cytoplasmic Asynchrony	87.1	72.0	81.3	79.1
Giant Metamyelocytes	78.6	82.0	85.9	72.8
Erythroid Hyperplasia	94.3	42.0	69.5	84.0

Discussion:

The present study compared the potential role for bone marrow examination in the differentiation of megaloblastic anemia (MA) from myelodysplastic syndrome (MDS) in 120 patients with macrocytic anemia and cytopenias. The clinical, hematological and marrow morphological features of both disorders are often overlapping and may create a diagnostic dilemma. The results of this study indicate the value of careful bone marrow examination in differentiating these entities and guiding clinical management. The present study demonstrated that 58.3% of cases were with megaloblastic anemia while 41.7% were with myelodysplastic syndrome. The predominance of megaloblastic anemia among patients presenting with cytopenias is also consistent with recent bone marrow-based observations. Kachhawa *et al.* reported megaloblastic anemia as the most frequent diagnosis among patients with pancytopenia, although myelodysplastic syndrome accounted for a smaller proportion of cases **[13]**. This relative enrichment of megaloblastic anemia is similar to that reported from developing nations in which vitamin B12 and folate deficiencies continue to be important causes of macrocytic anemia. Nutritional megaloblastosis is still a significant diagnostic consideration in patients with pancytopenia and macrocytosis, although MDS is becoming more known throughout the world. Previous published reports have highlighted the need for always attempting to rule out a reversible cause of dysplasia prior to making a diagnosis of MDS, as incorrect diagnosis can result in treatment for MDS which may cause unnecessary psychological distress for patients **[2]**. The age distribution was very different for the two groups. Patients had a significant age difference between MDS (63.4 ± 10.8 years) and megaloblastic anemia (41.8 ± 12.6 years) ($p<0.001$). This is consistent with the current knowledge that MDS is a disease of the elderly that is caused by acquired clonal abnormalities of the hematopoietic cells and age related genomic changes **[4]**. Recently, the role of molecular and cytogenetic abnormalities in the pathogenesis and classification of MDS has been further highlighted by the WHO and International Consensus Classification systems **[14, 15]**. There was a high

degree of overlap in clinical symptoms. Anemia is a prominent and ubiquitous feature of impaired hematopoiesis, which led to pallor and fatigue in both groups. Among the patients with MDS, however, there were significantly more patients with fever and bleeding manifestations. The results were probably indicative of more severe neutropenia and thrombocytopenia related to the clonal marrow dysfunction. Neurological symptoms were more common in megaloblastic anemia and were correlated with the vitamin B12 deficiency. The results are clinically useful, as neurological involvement is rare in MDS and could be a useful clue to nutrition deficiency **[5]**. Patients with megal oblastic anemia had significantly higher mean corpuscular volume values, as shown by hematological parameters. The severe macrocytosis and high serum lactate dehydrogenase were characteristic features of MA. LDH has been well recognized as a marker of ineffective erythropoiesis and destruction of erythroid precursors within the marrow. These findings corroborate previous studies reporting significantly elevated LDH and severe macrocytosis as a predisposing factor for the diagnosis of megaloblastic anemia as opposed to MDS **[7]**. The most significant finding of the present study is that of bone marrow morphology. In both disorders, hypercellular marrow was found, suggesting that marrow cellularity is not enough to differentiate. A few morphological traits showed high discriminatory power, however. There was significant association between erythroid hyperplasia, megaloblastic maturation, nuclear-cytoplasmic asynchrony and giant metamyelocytes with megaloblastic anemia. These manifestations are typical of defective synthesis of DNA due to vitamin B12 or folate deficiency. Similar findings have been noted in nutritional anemias that are evaluated with marrow morphology, wherein nuclear maturation defects are the hallmark of megaloblastic hematopoiesis **[8]**. In the present study, blood tests of megaloblastic maturation proved to be very sensitive and very specific for the diagnosis of MA. Another finding was nuclear-cytoplasmic asynchrony, which was also very consistent. These morphologic characteristics remain important and persist even in this era of sophisticated molecular diagnosis. It has also been emphasized that bone marrow examination remains the gold standard in the diagnostic evaluation of unexplained cytopenias, with morphological assessment forming the central component of MDS diagnosis **[16]**. Conversely, however, MDS patients had significantly elevated blast percentages, ring sideroblasts, Dysmegakaryopoiesis and dysgranulopoiesis. Numerous dysplastic megakaryocytes (micromega karyocytes and hypo lobated forms) were highly suggestive of MDS. Multilineage dysplasia is still one of the most important diagnostic features of MDS in the modern classification of WHO and ICC and has a significant role in the classification and prognosis of MDS **[11, 15]**. One of the salient points of the present study was the presence of the dysplastic changes in a part of patients having megaloblastic anemia. Multinuclearity, nuclear budding, abnormal granulocyte maturation and other morphologic abnormalities can result from nutritional deficiencies and mimic MDS. This is a commonly occurring phenomenon and is an important diagnostic dilemma. Therefore, marrow morphology is always evaluated in conjunction with biochemical assays such as serum vitamin B12 and folate level **[12]**. The diagnosis of MDS has greatly improved in recent years with the advent of molecular diagnosis. Clonal hematopoiesis is observed in mutations of genes including SF3B1, TET2, DNMT3A and ASXL1 which are thought to contribute to risk stratification. Research assessing molecular markers has shown them to be very useful for diagnostic and prognostic purposes in patients with unexplained cytopenias **[12, 17]**. However, not all healthcare facilities will have molecular testing readily available. Hence bone marrow aspiration and trephine biopsy remain the cost effective and widely available diagnostic techniques which can yield useful diagnostic information. Additionally, flow cytometric investigations have shown typical defects in the maturation of hematopoietic cells in both MDS and megaloblastic anemia. In recent years, recent evidence indicates that flow cytometry could be used in conjunction with morphological examination and increase the diagnostic accuracy, especially in cases in which the features are overlapping **[18]**. Morphology is the basis for interpretation of other modalities, however. The strengths of the present study are the relatively large sample size and the detailed evaluation of the clinical, hematological and marrow morphological parameters. This study, however, was limited by the single center design and the lack of comprehensive cytogenetic and molecular analysis. Advanced genomic investigations may give further clues in challenging diagnostic situations in future, multicentric studies. The present study findings overall indicate that BM is the key for the diagnosis of MDS versus megaloblastic anemia. Specific morphologic patterns achieved by recognition, along with clinical and biochemical correlation, allows for accurate diagnosis, avoiding misclassification and allowing for timely institution of appropriate therapy. This is important because megaloblastic anemia is a nutritional disease that can be reversed, whereas MDS is a disease of the mutated stem cells that needs to be monitored and treated over time.

Conclusion:

Bone marrow examination reliably differentiated megaloblastic anemia from myelodysplastic syndrome despite their overlapping clinical and hematological presentations. Megaloblastic maturation, nuclear-cytoplasmic asynchrony, erythroid hyperplasia and giant metamyelocytes favored megaloblastic anemia, whereas dysgranulopoiesis, dysmegakaryopoiesis, ring sideroblasts and increased blasts characterized myelodysplastic syndrome. Detailed bone marrow morphological assessment provides a cost-effective approach for accurate diagnosis and appropriate treatment selection in patients with macrocytic anemia and cytopenias.

References:

[1] Li H *et al. Nat Rev Dis Primers.* 2022 **8**:74. [PMID: 36396662]
[2] Sekeres MA & Taylor J. *JAMA.* 2022 **328**:872. [PMID: 36066514]

[3] Odenike O *et al. Clin Lab Med.* 2011 **31**:763. [PMID: 22118747]
[4] Hasserjian RP *et al. Blood.* 2023 **142**:2247. [PMID: 37774372]
[5] Garcia-Manero G. *Am J Hematol.* 2023 **98**:1307. [PMID: 37288607]
[6] Oster HS *et al. Haematologica.* 2025 **110**:300. [PMID: 39445407]
[7] Valent P *et al. Oncotarget.* 2017 **8**:73483. [PMID: 29088721]
[8] Prajapati A *et al. GAIMS J Med Sci.* 2024 **4**:35. [DOI: 10.5005/jablm-11031-0007]
[9] Zini G. *Ann Lab Med.* 2017 **37**:465. [PMID: 28840983]
[10] Tria FP 4th *et al. Diagnostics (Basel).* 2022 **12**:1581. [PMID: 35885487]
[11] Brunner AM *et al. Blood Cancer J.* 2022 **12**:166. [PMID: 36517487]
[12] He R *et al. Blood Cancer J.* 2022 **12**:12. [PMID: 35078969]
[13] Kachhawa GP *et al. J Appl Biochem Lab Med.* 2025. [DOI: 10.5005/jablm-11031-0007]
[14] Khoury JD *et al. Leukemia.* 2022 **36**:1703. [PMID: 35732831]
[15] Arber DA *et al. Blood.* 2022 **140**:1200. [PMID: 35767897]
[16] Oster HS & Mittelman M. *Front Oncol.* 2024 **14**:1415101. [PMID: 39346739]
[17] Obrebski T *et al. J Biol Chem.* 2026 **302**:111267. [PMID: 41655693]
[18] Briones V *et al. Colomb Med (Cali).* 2023 **54**:e2005494. [PMID: 37649984]

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