International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(4): 80-85
Received: 07-08-2021
Accepted: 09-09-2021

Dr. Shabnam Roohi
Consultant and Head, Department of Laboratory Medicine, SAKRA World Hospital, Bengaluru, Karnataka, India

Dr. Deepthi P Kambi
Associate Consultant, Department of Laboratory Medicine, SAKRA World Hospital, Bengaluru, Karnataka, India

Corresponding Author:
Dr. Deepthi P Kambi
Consultant and Head, Department of Laboratory Medicine, SAKRA World Hospital, Bengaluru, Karnataka, India

Myelodysplasia: A report of 6 cases

Dr. Shabnam Roohi and Dr. Deepthi P Kambi

DOI: https://doi.org/10.33545/pathol.2021.v4.i4b.425

Abstract
Introduction: Myelodysplasia is a typical feature of Myelodysplastic Syndrome (MDS), but not restricted to MDS, it may be found in non-clonal hematological as well as non-hematological diseases. The essential component of the WHO definition of MDS is the clonal nature of myelodysplastic hematopoiesis. MDS needs to be separated from the numerous neoplastic and non-clonal hematologic disorders mimicing MDS, because, while MDS is potentially preleukemic, disorders with secondary myelodysplasia are not neoplastic or preleukemic and are reversible when the underlying factor is removed.
Methods: We carried out an analysis of 6 cases presenting with marrow dysplasia between Feb2018 to Apr2019 and present their diagnostic approach with clinical history, complete blood count, biochemical tests, peripheral smear, bone marrow aspirate and biopsy, flowcytometry and cytogenetics.
Results: We hereby present a series of 6 cases of myelodysplasia. Two cases are primary MDS with clonality established. One case is associated with acute leukemia, and one therapy-related, and two cases secondary to an autoimmune disorder.
Conclusion: MDS is diagnosed by exclusion, because numerous signs of dysplasia might also occur in the context of other, including non-hematological diseases. It is therefore important to exclude other hematological and non-hematological diseases by a combination of clinical features, blood tests and molecular studies.

Keywords: Myelodysplasia, hematopoiesis, cytogenetics

Introduction
Myelodysplasia refers to dysplasia in one or more of the major myeloid cell lines of hematopoiesis. Although a typical feature of Myelodysplastic Syndrome (MDS), Myelodysplasia is not restricted to MDS; it may be found in non-clonal hematological as well as non-hematological diseases. The WHO definition of MDS states "The myelodysplastic syndromes (MOS) are a group of clonal haematopoietic stem cell diseases characterized by cytopenia, dysplasia in one or more of the major myeloid lineages, ineffective haematopoiesis, recurrent genetic abnormalities and increased risk of developing acute myeloid leukemia (AML)." Here, the essential component of the WHO definition of MDS is the clonal nature of myelodysplastic hematopoiesis. MDS needs to be separated from the numerous neoplastic and non-clonal hematologic disorders mimicking MDS, because, while MDS is potentially preleukemic, disorders with secondary myelodysplasia are not neoplastic or preleukemic and are reversible when the underlying factor is removed1.

Methods
We carried out an analysis of 6 cases presenting with marrow dysplasia between Feb2018 to Apr2019 and present their diagnostic approach with clinical history, complete blood count, biochemical tests, peripheral smear, bone marrow aspirate and biopsy, flowcytometry and cytogenetics.
The morphological hallmark of MDS is dysplasia in one or more myeloid lineages. Myelodysplasia may present in the form of dyserythropoiesis, dysmyelopoiesis or dysmegakaryopoiesis.

Table 1: Features of myelodysplasia in the three cell lineages

Dyserythopoiesis	Nuclear – budding, bridging, karyorrhexis, mitoses, multinuclearity, hyperlobation, megaloblastic change Cytoplasmic – budding, bridging, ring sideroblasts, vacuolization, PAS+
Dysmyelopoiesis	Small or unusually large, hypolobation, irregular hypersegmentation, agranularity or hypergranularity, Auer rods
Dysmegakaryopoiesis	Micromegakaryocytes, hypolobation, multinucleation

The major problem a pathologist faces is to decide whether the myelodysplasia is clonal (MDS) or polyclonal (Secondary myelodysplasia). There are various non-clonal, hematological as well as non-hematological disorders causing dysplasia in any of the cell lineages.

- VIT B12/Folate deficiency
- HIV
- Heavy metal poisoning
- Drugs
- Chemotherapy / Radiation
- Autoimmune disorders – SLE, ITP
- CDA
- Parvovirus infection

Therefore, it is extremely important to correlate the morphological findings with the clinical presentation and any pertinent family history.

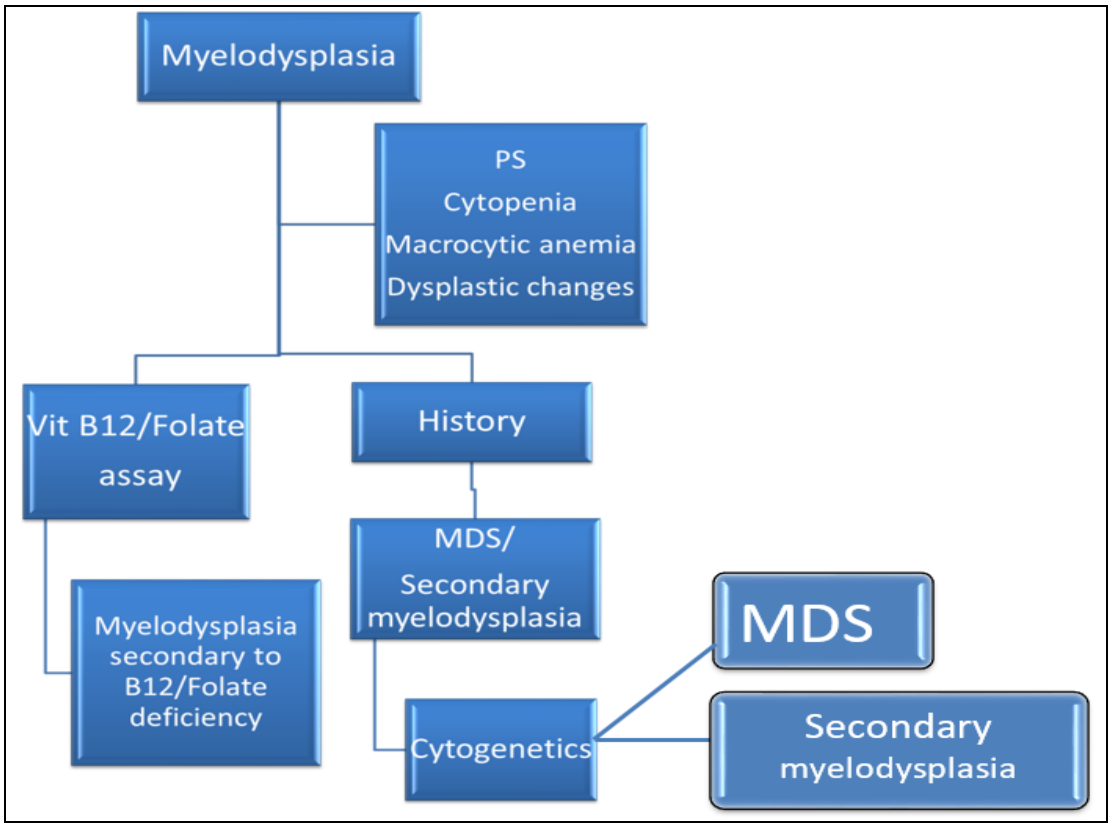


Fig 1: Approach to a case of Myelodysplasia

Case discussion

Case 1: 60 years male presenting with Macrocytic anemia Bone marrow examination was carried out in view of elderly patient with history not pointing to secondary factors of myelodysplasia and normal B12 levels. Marrow was hypercellular showing bilineal dysplasia. Cytogenetic studies showed 5q deletion (Figure 2). This was a case of 5q del syndrome.

Case 2: 41 years male presenting with persistent pancytopenia and dysplastic changes were observed on peripheral smear. Bone marrow aspirate showed hypercellular particle with trilineage dysplasia. Perls' stain for iron stores showed about 22% ringed sideroblasts. Cytogenetic study revealed a male karyotype with inverted duplication in the long arm of chromosome 1 (46XY, dup (1)(q32q21). We arrived at a diagnosis of Refractory Cytopenia with Multlineage Dysplasia -Ring sideroblast (RCMD-RS).

Case 3: 75 years male presenting with generalised weakness and pallor. Peripheral smear showed anisocytosis with macrocytic erythrocytes, nRBCs with dyserythropoietic changes, mild leukocytosis with dysplastic changes and increased blasts (16% myeloblasts) – suggestive of MPN or MDS with excess blasts. Bone marrow examination showed 56% myeloblasts with trilineage dysplasia and reticulin fibrosis. Flowcytometry confirmed the myeloid nature of the blasts and cytogenetics revealed male karyotype with decreased length of heterochromatin region in the long arm of Y chromosome (46XY, Yqh-[15]). The patient was diagnosed as MDS with excess blasts.

Case 4: 46 yrs male known case of CA colon on chemotherapy. On peripheral smear there was features of combined nutritional deficiency anemia with dysgranulopoiesis. In view of normal B12, bone marrow examination was performed which showed hypercellular marrow with megakaryocytic hyperplasia and trilineage

dysplasia. Cytogenetics was normal, hence MDS was ruled out and a final diagnosis of Therapy-related myelodysplasia was made.

Case 5: 33 years female, a known case of SLE presenting with pancytopenia. Bone marrow aspirate showed bilineage dysplasia (dysmyelopoiesis and dysmegakaryopoiesis) with lymphocytic aggregates and reticulin fibrosis on biopsy. Cytogenetics was normal, hence a case of myelodysplasia, secondary to SLE. Table 2 provides differentiating features between MDS (MDS-RA) and SLE (2) (3).

Table 2: Differentiating features between MDS (MDS-RA) and SLE

SLE	MDS
• Dysmyelopoisis with left shift • Bone marrow necrosis • Dilated sinuses(20%), stromal edema • Increased reticulin • Polyclonal lymphocytic aggregates	• ALIP • Inflammatory vascular damage • Microvascular obstruction by thrombus plugs

Case 6: 9 years male, a known case of ITP on steroids, presenting with pancytopenia, including severe thrombocytopenia. Bone marrow examination revealed hypocellular marrow showing trilineal dysplasia, reactive changes and mild hemophagocytosis. Cytogenetics was normal, hence the diagnosis Secondary myelodysplasia associated with autoimmune disorder (ITP). Table 3 provides differentiating features between MDS (RCC, RCUD, RCMD with unilineage cytopenia as thrombocytopenia) and chronic ITP.

In children, in the setting of hypocellular bone marrow with absence of cytogenetic abnormality, two bone marrow biopsies at least two weeks apart are necessary (2)(4)(5)

Table 3: Differentiating features between MDS (RCC, RCUD, RCMD with unilineage cytopenia as thrombocytopenia) and chronic ITP

ITP	MDS with isolated thrombocytopenia (RCC, RCUD, RCMD, MDS-U)
• Increased destruction of platelets • myelo & megakaryocytic dysplasia • megakaryocyte apoptosis • response to splenectomy	
Megakaryocyte apoptosis in stage3	• Apoptosis at micromegakaryocyte level • Apoptosis in myeloid, lymphoid and monocytic cell lines

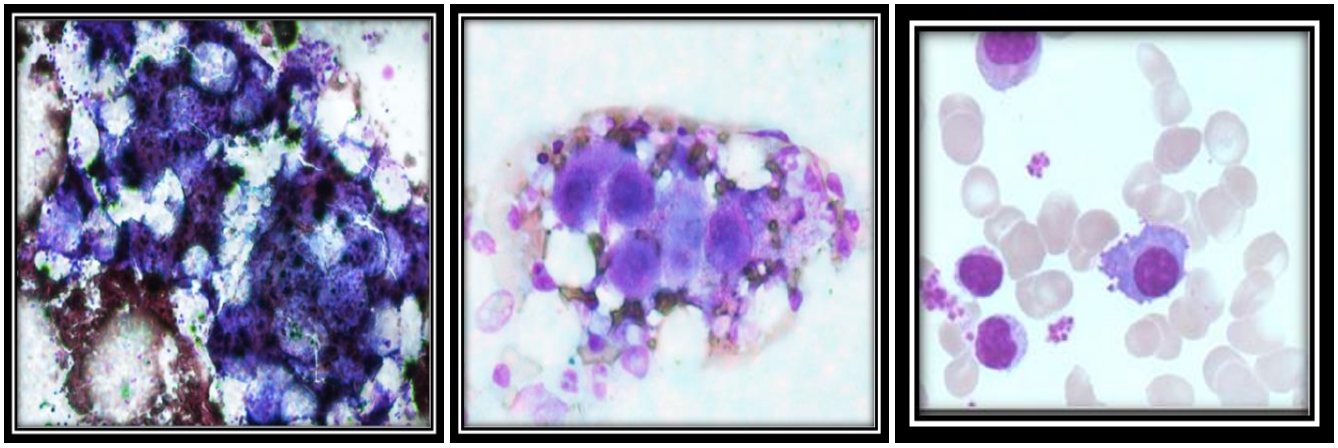
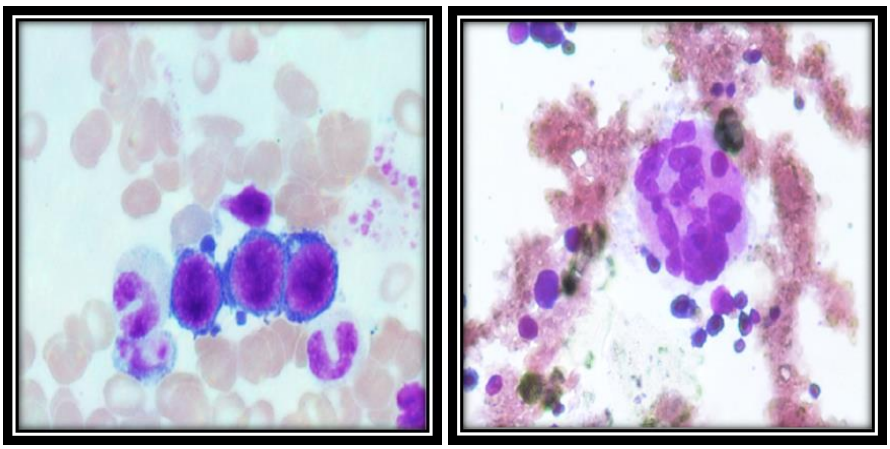


Fig 2: Case 1: Hypercellular marrow showing dysmegakaryopoiesis and dyserythropoiesis



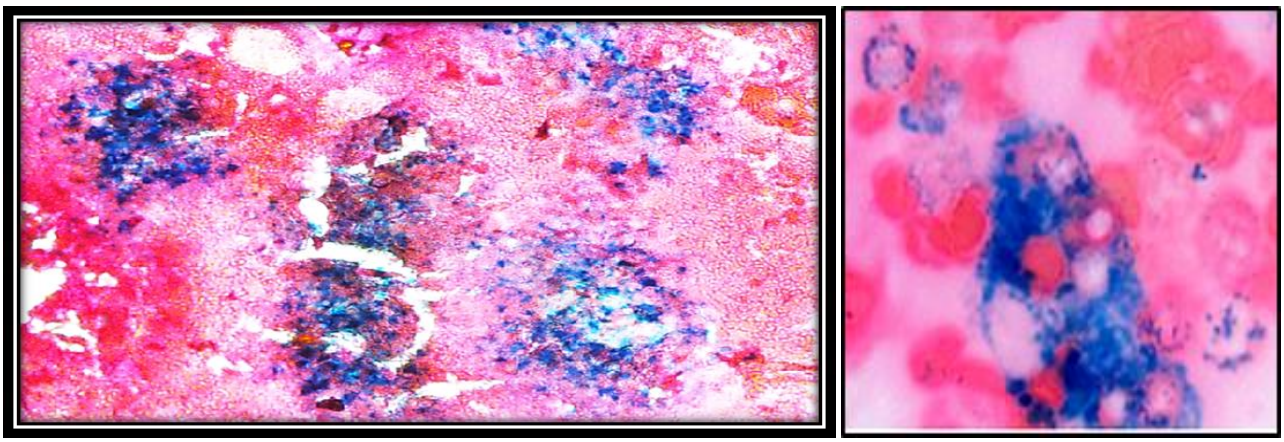


Fig 3: Case 2: Marrow showing dyserythropoiesis and dysmegakaryopoiesis. Perls' stain shows increased iron stores with 22% ringed sideroblasts (MDS-RS-MLD)

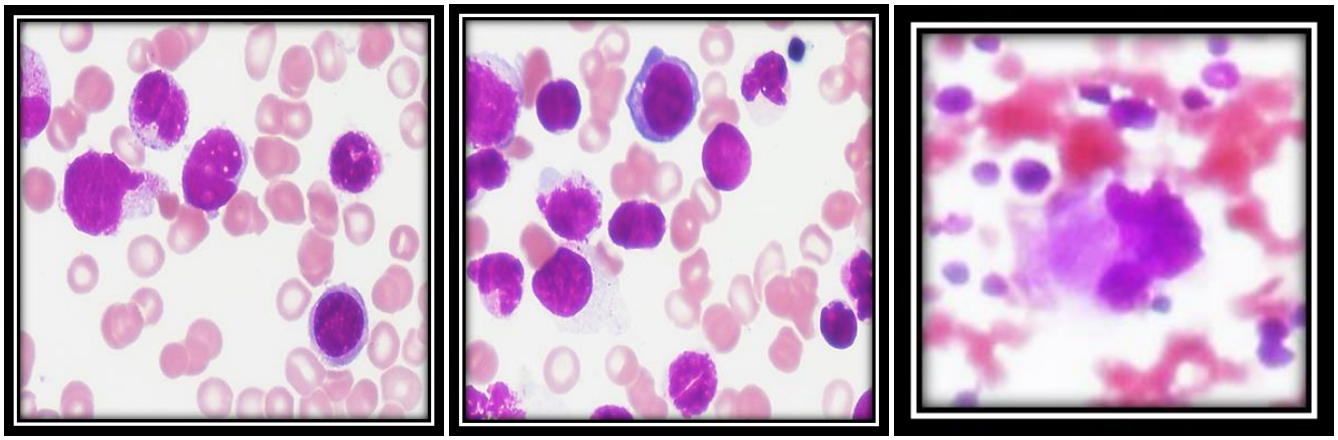


Fig 4: Case 3: Bone marrow aspirate showing 56% myeloblasts with trilieage dysplasia

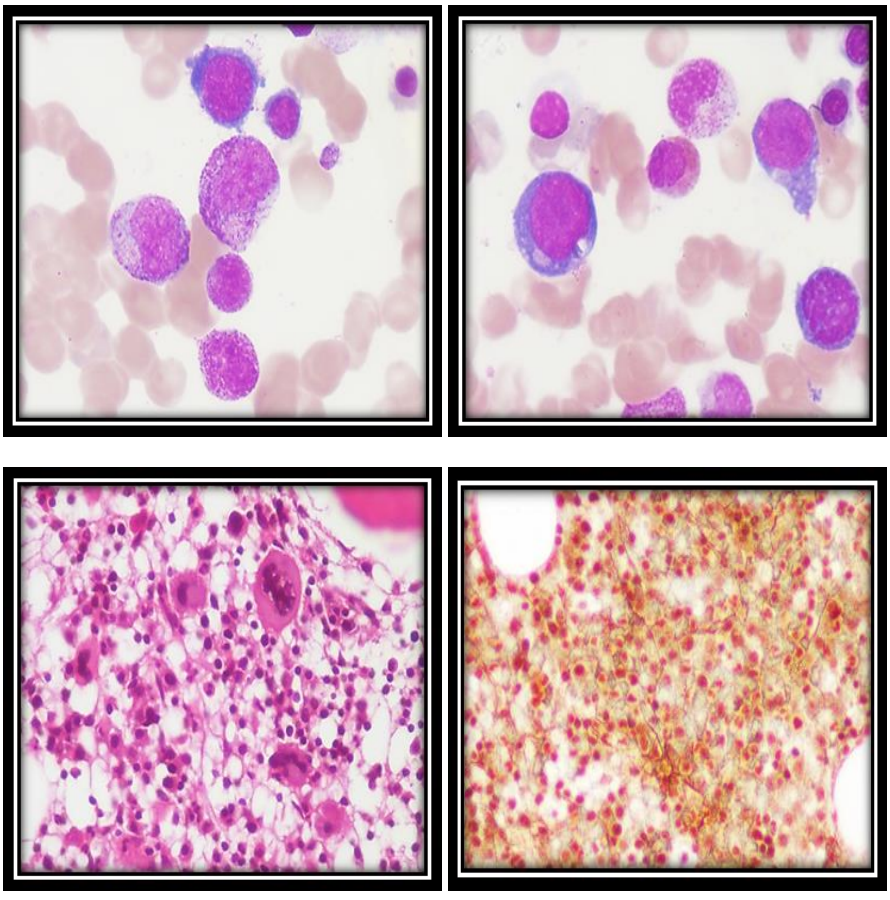


Fig 5: Case 4: Bone marrow aspirate showing trileage dysplasia. Bone marrow biopsy showing megakaryocyte hyperplasia and reticulin fibrosis

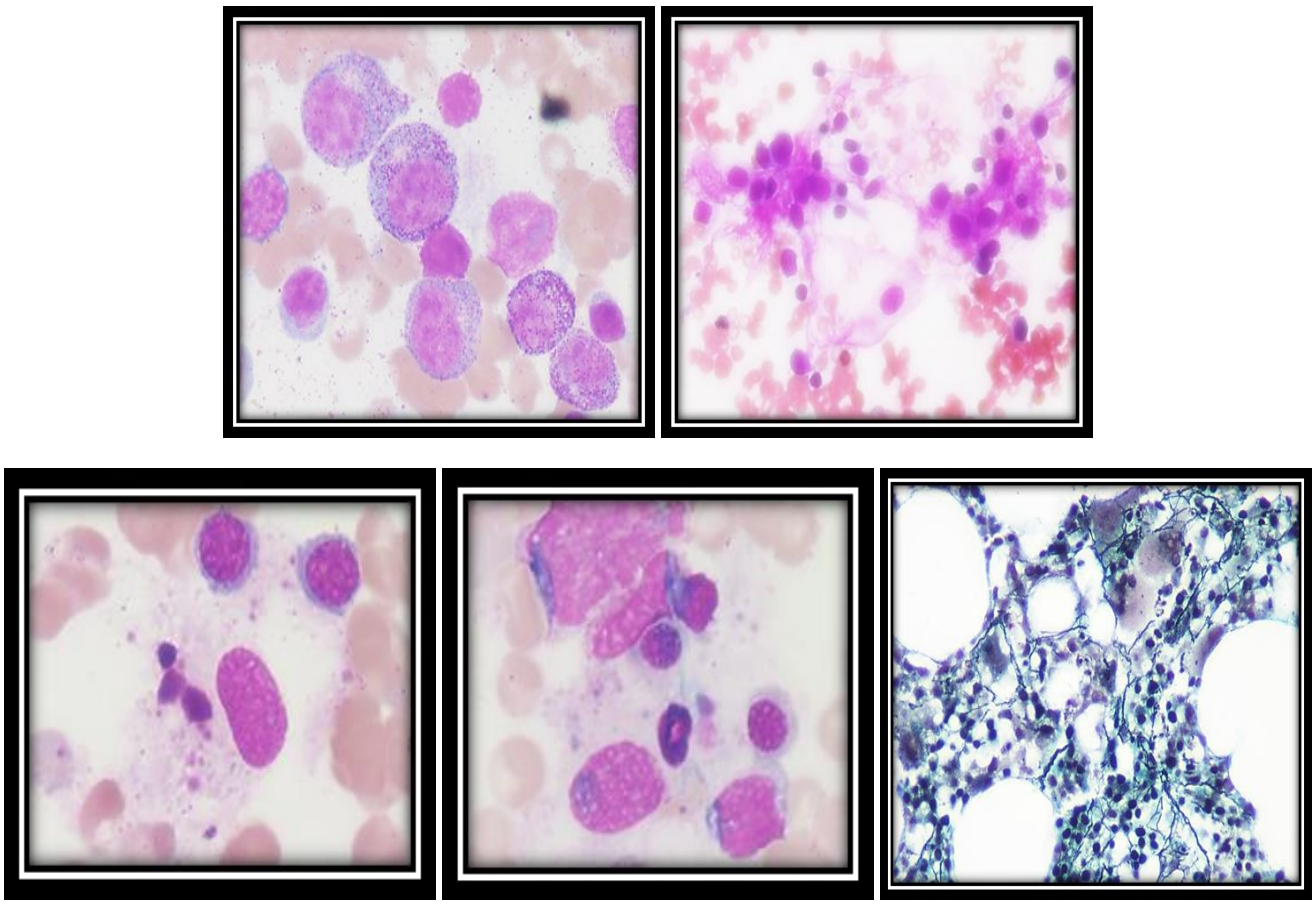


Fig 6: Case 5: Bone marrow aspirate showing bilineage dysplasia with reactive changes and hemophagocytosis. Reticulin stain on trephine biopsy showing increased fibrosis

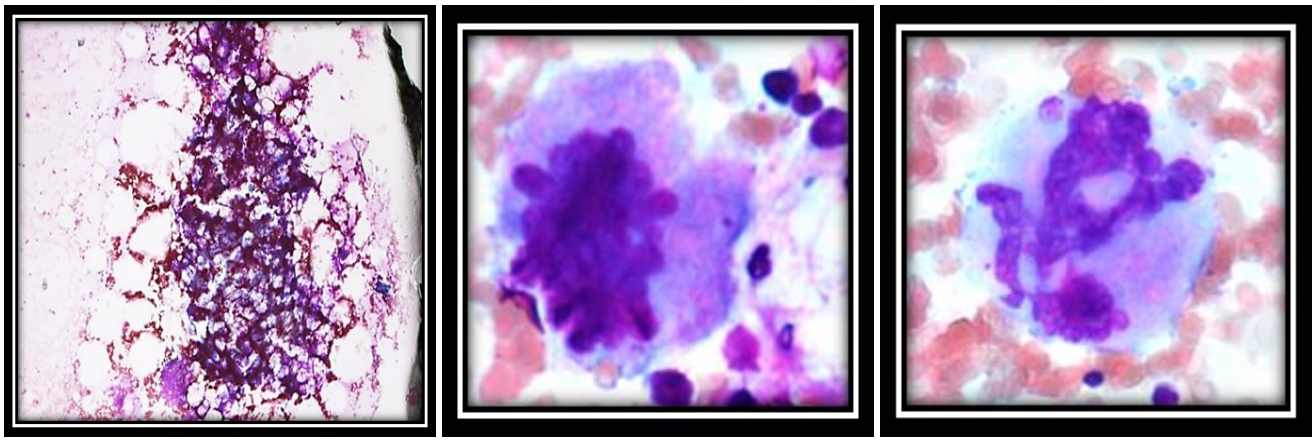


Fig 7: Case 6: Bone marrow aspirate showing hypocellular marrow and prominent dysmegakaryopoiesis

Conclusion

MDS is diagnosed by exclusion, because numerous signs of dysplasia might also occur in the context of other, including non-hematological diseases. It is therefore important to exclude other hematological and non-hematological diseases by a combination of clinical features, blood tests and molecular studies. As a heterogeneous disease with a nonspecific and highly variable clinical presentation, MDS presents a diagnostic challenge that requires careful assessment and a comprehensive workup.

The diagnosis of MDS requires morphologic evidence of significant dysplasia (ie, ≥10 percent of erythroid precursors, granulocytes, or megakaryocytes) on peripheral blood smear, bone marrow aspirate, and bone marrow biopsy in the absence of other causes of dysplasia. In the absence of morphologic evidence of dysplasia, a presumptive diagnosis of MDS can be made in patients with otherwise unexplained refractory cytopenia in the presence of certain genetic abnormalities.

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