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A Case of Myelodysplastic Syndrome: Rare Hypercellular Bone Marrow Feature

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Abstract:

Background: Myelodysplastic syndrome (MDS) is a broad array of hematological conditions defined by peripheral cytopenia, dysplastic hematopoietic progenitors, normal or hypercellular or hypocellular bone marrow, and a high risk of transition to acute myeloid leukemia.

Case Report: During a regular follow-up, a 59-year-old female patient presented to our hospital with complaints of fatigue and a severe headache. A complete blood count was performed, and it was reported that the patient had pancytopenia, which was persistent. Iron, folic acid, and vitamin B12 levels in the blood were extremely low, while LDH and ferritin levels were extremely high. A biopsy revealed that the patient had hypercellular bone marrow with dyspoiesis of the cells, excess blasts in immunohistology, and a 5-q deletion in karyotyping. The patient was then diagnosed with myelodysplastic syndrome with rare hypercellular characteristics.

Conclusion: Blood transfusions and immunomodulating medications like azacytidine or decitabine are the treatments. Regular monitoring of hematological symptoms is needed to prevent the progression of the disease.

Keywords: refractory pancytopenia, hypercellular bone marrow, dyspoiesis, 5q deletion, immunomodulating agents.

Introduction:

MDS is a heterogeneous category of hematologic diseases distinguished by cytopenia caused by bone marrow failure and an increased probability of becoming AML. Anemia, often associated with thrombocytopenia and neutropenia, is associated with dysmorphic (abnormally shaped) and generally cellular bone marrow, indicating inefficient blood cell generation. Clinical features of anemia (pallor, weakness, and fatigue), neutropenia (fever and opportunistic infections), and thrombocytopenia (increased bruising, petechiae, epistaxis, and mucosal bleeding) may be present. MDS progresses as bone marrow failure, characterized by infections, hemorrhagic, and anaemia-related comorbidities. The risk of developing myelodysplastic syndromes increases with age, as the disease is known to typically impact elderly people over the age of 60. The number and depth of cytopenia, percentage of bone marrow blasts, cytogenic abnormalities, anemia severity, and transfusion requirement all determine the prognosis of MDS patients. The treatment aims to delay the disease progression through genuine chemotherapy, demyelinating agents, and blood transfusions.[1]

This patient has been on follow-up for diabetes for the preceding four years and had recently developed pancytopenia. She was sent to a tertiary care center for additional testing and was diagnosed with myelodysplastic syndrome. Although this is a rare syndrome that often affects the elderly, our patient is less than 60 years along with diabetes and hypothyroidism as co-morbidities. She also recovered completely from a minor COVID 19 infection in July 2021. Even if she had a covid 19 infection, the potential of a correlation is remote because her prior diagnosis of anemia was in June 2021.

As it's typical even among professionals, the diagnosis was delayed for three months due to vague symptoms of the illness that may have been attributed to simple nutritional deficiency anemia or uncontrolled diabetes. When she was found to have worsening anemia, a peripheral smear was

done, which revealed that her RBCs were larger and there was pancytopenia. A detailed workout in tertiary care hospital yielded the diagnosis of MDS.

Case report:

A 59-year-old-lady with Diabetes Mellitus and Hypothyroidism on treatment presented to us on December 6, 2020, with severe headache and fatigue complaints. We diagnosed Pancytopenia (values in table 1) and referred her to a tertiary center for further evaluation. In the meanwhile, she got infected with COVID-19 and recovered.

Table 1 Shows the consecutive pancytopenia for several months

	12/06 /2021	08/07 /2021	10/07 /2021	27/08 /2021	16/09 /2021
Haemoglobin (g/l)	8.7	5.7	11.9	8.9	7.1
Red Blood Cells (* 10^{12}/L)	3.12	1.9	4.0	3.2	2.5
White Blood Cells (*10^9/L)	3.8	2.4	2.8	3.7	2.9
Platelets (*10^9/L)	2.9	1.4	1.3	1.1	2.2

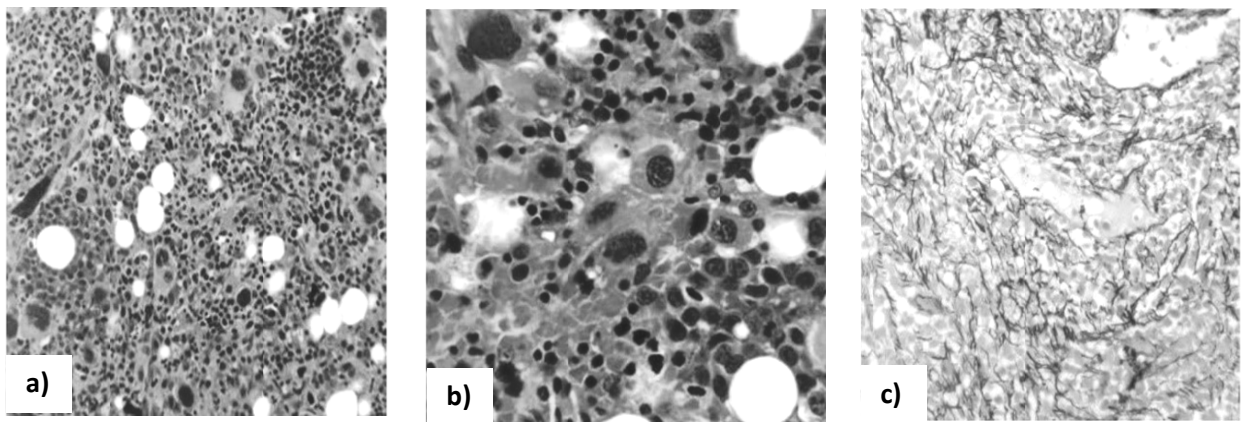
She complained of widespread abdominal discomfort and epigastric pain on 08/07/2021, but there was no disruption in her bowel or bladder habits. The vital signs are normal. Her HbA1c level is 7.1. Her PT was 18 seconds, and her INR was 1.28. Urine analysis revealed that it was normal. The abdomen and pelvis's plain and contrast CT scans were normal except for uterine fibroid with calcification and atrophic ovaries. Upper Gastro-Intestinal Endoscopy was significant for gastritis with a positive Rapid Urease test. The patient has then prescribed antibiotics against H. pylori and multi-vitamins for ten days.

The hematologist recommended checking the levels of LDH, serum iron, ferritin, folic acid, and vitamin B12 and do a peripheral smear. The levels of LDH (467 U/L) and ferritin (418.4 ng/ml) were high. Iron (78.5 g/dl), folic acid (1.34 ng/ml), and vitamin B12 were low. A peripheral smear revealed Pancytopenia. In peripheral smear, RBCs were decreased in number, macrocytic and normochromic suggestive of megaloblastic anemia, leukopenia, and thrombocytopenia.

On August 27, 2021. She had come with complaints of abdominal pain, back pain, and leg pain for the preceding four months. On examination, there was no hepatosplenomegaly, but there was pallor. The hematologist advised blood transfusions and vitamin B complex for a week. Even after blood transfusions and correction of Vitamin B12 deficiency, the Complete Blood Count (CBC) showed only mild improvement. A bone marrow aspiration, biopsy, and karyotyping were recommended for further evaluation.

Bone marrow aspiration with trephine biopsy:

Figure 1 a) Hypercellular with 10-12 inter-trabecular spaces. b) Megakaryocytes are increased in number and show prominent dyspoieis in the form of micro megakaryocytes, Mono lobated, hypo lobated and hyperchromatic nuclei and



Erythroid series cells are preponderant and Myeloid series cells show all stages of maturation with a few intermixed blasts. C)Reticulin stain: Diffuse increase in reticulin fibres with intersections and focal thick bundles corresponding to WHO- MF-2/3.

Immunohistology:

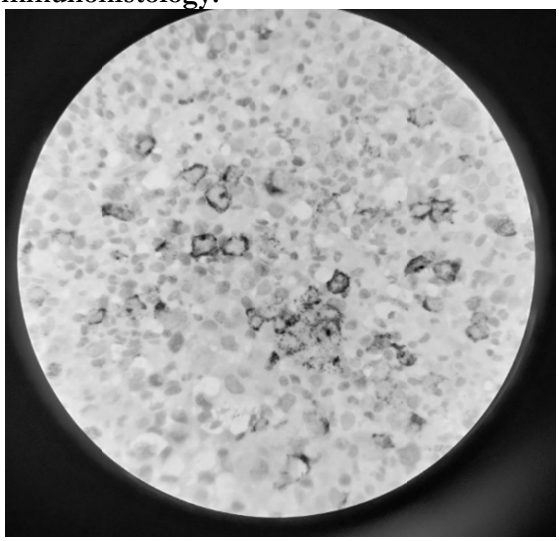


Figure B Myelodysplastic syndrome with excess blasts (CD-34 positive cells) and fibrosis.

Cytogenetic Report:

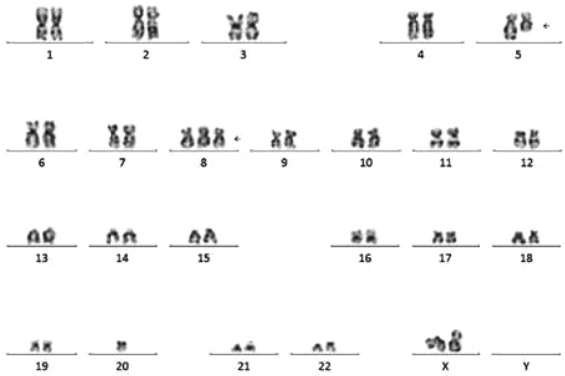


Figure C Karyotyping indicates 5q deletion.

0n 16/09/2021, her bone marrow aspirate revealed hypercellularity and dyspoiesis. (Figure:1) Immunohistochemistry revealed MDS with an excess of blasts (CD-34 positive cells) and fibrosis. Figure:2). Karyotyping showed 5q deletion; 45, -X, t95;12) (q33.2; p13.2) [01]/46, XX, del (5) (933.2), +8, -20[35]/46, XX [04] (Figure:3) Erythropoietin levels were found to be significantly high 750 mIU/ml. Biopsy and karyotyping results indicated that the patient had Myelodysplastic syndrome with excess blasts and a 5q deletion chromosomal mutation. According to the World Health Organization (WPSS- Scoring system), it is categorized as Myelodysplastic syndrome - unclassifiable. The patient was given Thalidomide 50 mg, Prednisolone 20 mg, Folic acid 5 mg, Calcium, and Vit-D3 500IU. Pantoprazole 40 mg once a day. As her hemoglobin level was 7.9 g/l, she was given a blood transfusion.

Discussion:

Myelodysplastic syndromes are a spectrum of clonal hematopoietic stem cell disorders characterized by unique hematopoietic stem cell mutations, most often in RNA splicing genes.

It mostly affects the elderly and is characterized by one or more refractory cytopenia. The annual incidence per 100 000 population was estimated as 0.5 for people less than 50 years of age, and prevalence increased.[2] Risk increases with age due to the acquisition of somatic mutations that can promote clonal expansion and dominance of a specific hematopoietic stem cell. Typically, patients will die due to pancytopenia or progression to leukemia, although the majority will die because of concomitant diseases rather than bone marrow failure itself. According to the French-American-British group classification, our case report comes under Refractory anemia with excess blasts.[3] Scientific advances in cytogenetic research redefined WHO's classification of MDS. For convenience, a picture of the WHO categorization is included; it comes under the class of Myelodysplastic syndrome unclassifiable (MDS-U). [4,5,6]

An unknown etiology causes the myelodysplastic syndrome. MDS is caused by a sequence of genetic alterations in hematopoietic stem cells. These modifications affect normal cell growth and differentiation (development into different types of blood cells). This causes a build-

up of aberrant, immature cells in the bone marrow and a reduction in the production of new blood cells.[7]The genetic mutation may be induced by a hereditary propensity or by damage to a cell's DNA (a somatic mutation) caused by radiation, viral infection, or certain chemicals (e.g., benzene chemotherapy (particularly long or intense regimens involving alkylating agents, hydroxyurea, and/or topoisomerase inhibitors). Chromosomal abnormalities (deletions, duplications, and structural abnormalities) are common. When MDS develops because of prior therapy for another malignancy, it is referred to as "secondary" MDS.[8] Disordered cell production is also linked to morphologic cellular abnormalities in bone marrow and blood. Extramedullary hematopoiesis can develop, resulting in hepatomegaly and splenomegaly. Myelofibrosis can develop during MDS.

Primary MDS is of idiopathic origin. Our patient has characteristics of MDS Unclassifiable such as refractory cytopenia, anemia with excess blasts in the bone marrow and 5q deletion in the chromosome, pancytopenia with trilineage dysplasia, and high levels of erythropoietin. It has both the features of a subcategory of MDS unclassifiable such as MDS Pan and MDS CG.[9]

MDS associated with 5q deletion is uncommon, with a low risk of progression to AML and a high response rate to immunomodulatory drugs such as thalidomide and lenalidomide treatment. The presence of chromosomal abnormalities is included in the IPSS, and the results have major prognostic significance. Less than 5% of female patients exhibit erythropoietin-refractory anemia, thrombocytosis, and hypolobated cells.

The International Prognostic Scoring System (IPSS) considers the percentage of bone marrow blasts, the number of cytopenia, and cytogenetic abnormalities. Patients are categorized into four risk classes based on these variables. According to MDS foundation.org, the prognosis calculation for the progression of the disease to AML, the IPSS-R score, is 3.5, and the category is INTERMEDIATE for our patient. The survival estimation for age-related calculation is 3.14 and category is intermediate.[10,11]

Conclusion:

Myelodysplastic Syndrome becomes a life-threatening condition if there is a delay in diagnosis or if there is an improper follow-up of the disease progression. Our patient was found to be peculiar. Cytogenetics was abnormal (5q deletion) and bone marrow abnormality (hypercellular, dyspoiesis, refractory pancytopenia), along with high levels of erythropoietin. This falls under the category of Myelodysplastic syndrome unclassifiable (MDS PAN and CG). But according to the IPSS-R score, the risk of progression into AML was intermediate and had a better survival rate based on age. The therapeutic options were blood transfusion when Hb <7.9g/L and an immunomodulating agent such as thalidomide.

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