RESEARCH ARTICLE

ACQUIRED MARKED ELLIPTOCYTOYSIS IN MYELODYSPLASTIC SYNDROME: POSSIBLE ASSOCIATION WITH DELETION (20Q).

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Abstract:
Myelodysplastic Syndromes (MDS) are heterogeneous group of myeloid malignancies that result in bone marrow failure and peripheral blood cytopenias. Elliptocytes are most abundant in hereditary elliptocytosis. Isolated deletion 20q [del (20q)] associated with elliptocytosis in a patient of myelodysplastic syndrome is very rare and only few cases are reported in literature.
We report a case of 72 year old male presented with thrombocytopenia and anaemia and marked RBC elliptocytosis, diagnosed as refractory anaemia with multilineage dysplasia associated with isolated del (20q) on FISH analysis of bone marrow.
The presence of cytogenetic alterations have diagnostic and prognostic role. Deletion of the long arm of chromosome 20 [del (20q)] may be an early and primary genetic event in several haematological disorders. Chromosome 20q deletion is associated with about 5% of primary MDS.

Key Words: Myelodysplastic Syndrome, Cytogenetics, Thrombocytopenia, elliptocytosis.

Introduction:-
MDS is diagnosed based on the presence of dysplastic features in the peripheral blood and bone marrow. Elliptocytes are usually less than 5% of red blood cells in normal population. Mild to moderate number of elliptocytosis are frequent in various disorder such as iron deficiency, B12 /Folate deficiency, myeloproliferative disorder (MPD), myelodysplastic syndromes (MDS) and metastatic disease.[1] Thrombocytopenia (platelets<100x10(9)/L) in MDS is ranged from 40% to 65% and a dominant thrombocytopenic presentation in MDS is rare (3%–7%). [2, 3].

Diagnosis is supported by the presence of cytogenetic alterations and genetic mutations. Clonal chromosomal abnormalities, identified using metaphase cytogenetics, are seen in 30%–50% of patients with de novo MDS, and in up to 80% of cases with therapy-related MDS. These abnormalities are demonstrated using conventional cytogenetics and/or fluorescence in situ hybridisation (FISH). The most frequent single cytogenetic abnormalities include del (5q), monosomy 7 or del (7q), trisomy 8, and del (20q).

Deletion of the long arm of chromosome 20 [del (20q)] may be an early and primary genetic event in several haematological disorders such as MDS (most common), MPD, acute myeloid leukemia, angioimmunoblastic T-cell lymphoma with dysproteinemia and pure red cell aplasia. The occurrence of isolated del (20q) is a favorable prognostic marker in patients with MDS. It is characterized by an indolent clinical course and a significantly lower risk of progression to AML. [3] In MDS patients association of elliptocytosis and del 20q is very rare and acquired RBC elliptocytosis may point to del 20q.

Case Report:-
A 72-year-old man presented with fatigue and progressively increasing pallor for past 1 year. There were no symptoms of fever or bleeding. Past hematological assessment showed anaemia with progressive decrease in haemoglobin for which patient received Vitamin B12, folic acid and erythropoietin. Patient did not receive any blood transfusion. Physical examination showed pallor. There was no evidence of lymphadenopathy or hepatosplenomegaly. Complete Blood Counts revealed anaemia (Hb: 9 gm/dl, MCV: 80.3fL, MCH: 24.9pg, MCHC:
31.0g/dL, RDW: 12.8%), thrombocytopenia (Platelet counts 94 x 10^3 /uL) with normal TLC (4.43 x 10^9/L) and differential counts (Polymorphs – 44%, Lymphocytes 37%, Monocytes 16%, Eosinophils 03%, Basophils 00%). Peripheral smear showed RBC elliptocytosis (70% elliptocytes); however, there was no evidence of hemolysis. Peripheral smears reported thrice in past one year showed normocytic normochromic RBCs and had no mention of elliptocytosis. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total Bilirubin, Urea, Creatinine, electrolytes, Lipid profile, Iron profile, thyroid profile, Coombs test, G6PD, reticulocyte count and Hb HPLC were within normal limits. Bone marrow aspirate and biopsy showed hypercellular marrow (approximately 80% cellularity). There was megaloblastic erythroid hyperplasia. Granulocytic series showed cells at all stages of maturation with no evidence of significant dysgranulopoiesis. Megakaryocytes were increased and showed dysmegakaryopoiesis in form of dissociated nuclear lobes. Blast count on bone marrow aspirate was less than 2%. Perl’s stain on bone marrow aspirate showed adequate macrophage iron with no evidence of ring sideroblast. Bone marrow biopsy showed Grade 1 fibrosis on Reticulin stain. [Figure 1] Together with CBC, bone marrow aspirate and biopsy morphology; features were suggestive of Myelodysplastic Syndrome: Refractory cytopenia with multilineage dysplasia (MDS-RCMD).

FISH analysis with specific probes (5q31, 7q31, 20q12, centromere 8, and 11q23) revealed deletion of 20q12 locus in 64% (128/200) of nuclei examined. Conventional cytogenetics analysis by G-banding showed normal 46XY karyotype. [Figure 2]

Discussion:

In Myelodysplastic syndrome RBC morphology is usually normocytic, macrocytic or dimorphic. Elliptocytes, teardrops, stomatocytes, or acanthocytes may predominate, reflecting intrinsic alterations in cytoskeletal proteins. Several cytogenetics findings are associated with characteristic morphological abnormalities, such as hypolobate megakaryocytic in deletion (5q), pseudo Pelger -Huet anomaly in 17p loss and small vacuolated neutrophils in TP53 mutation in therapy-related MDS [4].

RBC elliptocytosis has been described as a rare RBC abnormality in MDS with isolated deletion (20q). Ishida et al, 1999, reported a patient with MDS who presented with elliptocytosis had mild anaemia and hypercellular bone marrow with three lineage dysplasia. Deletion of 20q and translocation (1; 5) (p10; q10) was detected by conventional karyotyping of bone marrow cells. [5] Hur M et al, 2004, reported acquired elliptocytosis occurred as an unusual morphological feature of MDS, associated with abnormalities of protein 4.1 and chromosome 20q,[6] Knight J et al, 2013 reported an association between elliptocytosis in MDS and del (20q) that was similar as in present case. Acquired elliptocytosis may be seen in a variety of bone marrow disorders such as fibrosis, myelophthisis, and dysplastic erythropoiesis in the setting of MDS. Diminished production of protein 4.1 (EBP41), a structural RBC protein implicated in some cases of HE, has also been demonstrated in MDS with elliptocytosis [7].

Karyotype is a strong independent prognostic factor and FISH may complement conventional cytogenetic analysis. FISH can detect abnormalities in up to 15% of karyotypically normal MDS patients. Case series published by Braun et al. revealed patients with isolated 20q deletion had significantly reduced marrow percentage of blasts, lower platelet count and higher reticulocyte count when compared with clinical features of patients without 20q deletion. MDS in patients with isolated 20q deletion was associated with features of low risk and favorable prognosis. [8] Gupta et al found that 7out of 9 patients of MDS with del (20q) commonly presents with thrombocytopenia and has minimal morphological dysplasia. [9]

In the present case patient presented with progressive anaemia followed by bicytopenia, marked acquired RBC elliptocytosis and bilineage dysplasia in marrow and found to have isolated del20q on FISH analysis, thus diagnosed as Refractory cytopenia with multilineage dysplasia.

Conclusion:

Acquired elliptocytosis associated with MDS with underlying del20q abnormality is a rare finding. Morphologic findings of peripheral smear can predict a possible underlying cytogenetic alteration in cases of MDS.

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Figure 1: A) Peripheral blood showing marked RBC elliptocytosis (Leishman stain, 20x). B) Bone marrow biopsy showing hypercellular marrow with reduced fat spaces. (H & E stain, 4x). C) Bone marrow biopsy showing marked erythroid hyperplasia and dysplastic megakaryocytes (40x). D) Reticulin stained sections of marrow biopsy showing Grade 1 fibrosis (40X).

Figure 2: 5q) Cell showing two green and two orange signals, indicating negative for deletion 5q33-q34; 20q) Cell showing one orange signal, indicating positive for deletion 20q12; 7q) Cell showing two green and two orange
signals, indicating negative for deletion 7q31; T8) Cell showing two green and two orange signals, indicating negative for Trisomy 8.

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