Case Report

A hapless case of 5q minus

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ABSTRACT

The 5q-syndrome is a myelodysplastic syndrome (MDS) characterized by a defect in erythroid differentiation. Patients have severe macrocytic anemia, normal/elevated platelet counts, normal/reduced neutrophil counts, erythroid hypoplasia, and hypolobated micro-megakaryocytes in the bone marrow. A thalidomide analogue, lenalidomide, induces transfusion independence and cytogenetic remission in a substantial number of patients. This case is presented for its rarity and therapeutic challenge. A postmenopausal female patient presented to the Outpatient Department with a history of progressive drop in hemoglobin and white blood cells for the last 6 months, for which she was on oral hematinics. The peripheral smear and bone marrow showed classical findings of pseudo-Pelger-Huet neutrophils and hypolobated megakaryocytes with no excess of blasts, respectively. Molecular studies were positive for 5q deletion (46, XX, del[5][q33q35]). Lenalidomide therapy was started, a year after starting treatment, the patient progressed to MDS with increased blasts-2 and subsequently to acute myeloid leukemia within 2 months. The karyotyping done at this time suggested evolution of a complex karyotype and presence of an additional translocation 46, XX, del (3) (q12), t (5;7) (q13; q22). The patient succumbed to multiple infections approximately 1.5 years after diagnosis.

Key words: 5q, Bicytopenia, Karyotyping, Lenalidomide, Monosomy 5, Myelodysplasia

The 5q-myelodysplastic syndrome (MDS) typically occurs in older age groups, particularly in females. Characteristic features are macrocytic anemia, normal or elevated platelets in the presence of megakaryocytic anomalies, and a mild clinical course [1]. Chromosome 5 abnormalities, deletion of the long arm of chromosome 5 (del[5q]), or monosomy 5 (−5), arise in about 10% of MDS, either as the sole cytogenetic abnormality or as part of a complicated karyotype, and have distinct clinical implications for MDS [2]. The 5q-syndrome is found predominantly in females of advanced age and has a good prognosis with <10% of patients transforming to acute myeloid leukemia (AML) [3]. Lenalidomide, a thalidomide analogue with immunomodulatory and anti-angiogenic properties, induces transfusion independence and cytogenetic response in a high proportion of patients with MDS and 5q deletion [4-7]. The risk of progression to AML is estimated to be low, at least for patients who do not have additional risk factors such as an elevated blast count, transfusion dependence, or additional chromosome aberrations [8].

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CASE REPORT

A 59-year-old postmenopausal female presented with refractory anemia and leucopenia. She had breathlessness on exertion, generalized weakness, and pedal edema.

On examination, the patient had stable vitals and was afebrile. The peripheral blood counts showed hemoglobin of 6.3 gm/dL and white blood cells count of 3790×109/L with a normal platelet count of 202×109/L and a reticulocyte count of 2.83%. The peripheral smear revealed macrocytic red cells and hypolobated neutropenia (pseudopelger-huet). Platelets were adequate in the smear.

Bone marrow aspirate and biopsy were performed for further evaluation of the bicytopenia, which revealed a normocellular marrow with an increase in megakaryocytes showing focal clustering. The megakaryocytes were small in size with characteristic hypolobation and non-lobation. The erythroid series was mildly reduced in number and showed megaloblastic maturation. No remarkable dysplasia was noted in the erythroid and myeloid series. Blasts were ~4% of all nucleated cells. No ring sideroblasts were seen.

In view of the bicytopenia and megakaryocytic dysplasia, a 5q deletion study, along with an MDS panel by fluorescence *in situ* hybridization (FISH), was advised.

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Interphase FISH analysis revealed loss of hybridization signal from both 5q31 and 5q33 probes, indicating deletion of 5q in 66% of interphases that were examined. G-band karyotyping study confirmed isolated 5q deletion as the sole abnormality, with karyotype of 46, XX, del (5) (q33q35). No other associated molecular abnormality, such as trisomy 8, deletion 7, or deletion 20, was detected.

Subsequently, the patient was started on Lenalidomide therapy and became transfusion independent/had an erythroid response within a few months. Bone marrow examination done after 6 months of diagnosis showed no excess of blasts (2–4%) and erythroid hyperplasia. Karyotyping done at this phase showed 46, XX, del 5q in the majority of the metaphases. 150/200 (75%) interphases showed a large 5q deletion in FISH. Hence, the patient had no cytogenetic remission after 6 months of lenalidomide therapy. Approximately 1-year post-diagnosis, routine peripheral smear examination revealed leucopenia with shift to the left and 7 % blasts (Fig. 1).

A bone marrow examination revealed ~15% blasts of myeloid phenotype on immunophenotyping. An impression of MDS with increased blasts −2/evolving AML in a known case of 5q deletion syndrome was given. Karyotyping revealed 46, XX, del (3) (q12), t (5;7) (q13; q22) against the primary karyotyping 46, XX, del (5) (q33q35) (Fig. 2).

The patient was started on combination chemotherapy with Azacytidine and venetoclax. Two months later, she was admitted with hematochezia and hematuria. Complete blood count showed marked thrombocytopenia with rising counts and progressively increasing blasts (Maximum of 52%). The patient was declared to have treatment failure, and she succumbed to multiple infections/septic shock approximately 1.5 years post-diagnosis of 5q-syndrome.

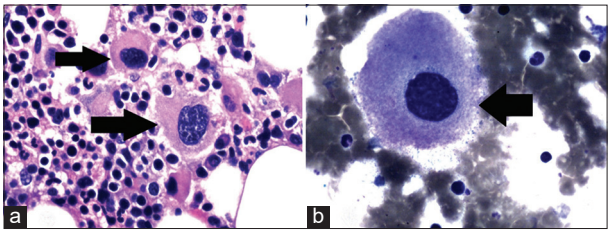

Figure 1: (a) Hypolobated megakaryocytes, (b) Monolobate megakaryocyte

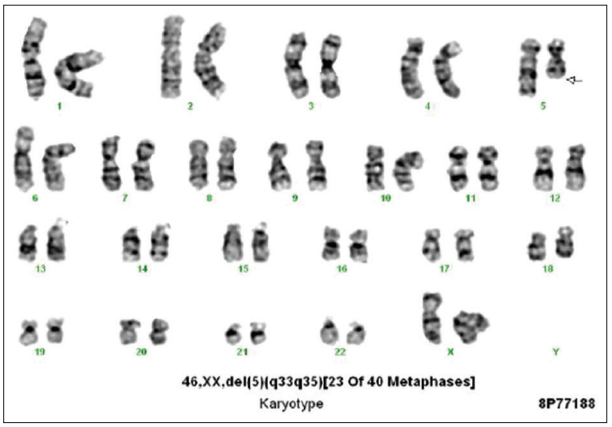

Figure 2: Primary karyotype 46, XX, del (5) (q33q35

DISCUSSION

5q deletion syndrome is recognized as a distinct entity defined by the World Health Organization classification of MDS with a clear genotype/phenotype relationship [3]. It has a female preponderance, showing good prognosis with <10% of patients transforming to AML [3-12].

Lenalidomide can reduce transfusion requirements and reverse cytologic and cytogenetic abnormalities in patients who have MDS with 5q deletion. Patients with continuous or transient erythroid response carry a significantly lower risk of progression to AML than patients without erythroid response [8]. Genetic instability and clonal evolution seem to be the driving forces of leukemic transformation in 5q-MDS patients treated with Lenalidomide. Close and careful cytogenetic follow-up even after reaching a complete cytogenetic response (CCyR) is of utmost importance, since the clone with 5q deletion may reappear, increase in size, and acquire additional chromosome aberrations, indicating progression of the disease [8].

CCyR is defined as the disappearance of the 5q deletion or any other chromosome aberration. Partial cytogenetic response is defined as a reduction of aberrant cells of more than 50% compared to the previous cytogenetic investigation; <50% is defined as having no CCyR [4]. Cytogenetic investigation should always include full karyotype analysis, since in many patients, loss of cytogenetic response is indicated by only one metaphase with 5q deletion, whereas FISH analysis may provide a negative result.

The complex karyotypes consist of characteristic aberrations like deletions of 7q, deletions of 17p, or trisomy 21. Inactivation of p53, the guardian of the genome with important functions in DNA repair and apoptosis induction, may be a critical early event during clonal evolution of 5q- clones, triggering genetic instability and the acquisition of secondary chromosome aberrations [13-15].

Our case had none of the additional risk factors of elevated blast count, transfusion dependence, or additional chromosome aberrations at the outset. The patient also had erythroid response, but no cytogenetic remission was achieved 6 months after starting Lenalidomide therapy. Subsequently, she progressed to AML within a year of starting treatment owing to the development of a complex karyotype.

CONCLUSION

As per studies, erythroid and cytogenetic responders to lenalidomide therapy had a significantly decreased risk of progression to AML. Hence, regular follow-up investigations of del(5q) MDS patients treated with lenalidomide may help to identify patients requiring alternative treatment strategies and provide information regarding long-term prognosis.

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