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Case Report
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Philadelphia Chromosome Positive Myelodysplastic Syndrome - A Rare Case Scenario

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Abstract

Introduction: Myelodysplastic Syndrome (MDS) is a group of acquired disorders characterized by ineffective and dysplastic hematopoiesis; We report a case of MDS with the Philadelphia translocation here which is rarely reported in patients with MDS and reviewed other similar cases.

Case Report: An elderly female was diagnosed with MDS-EB1 incidentally while undergoing PTCA. The AML and MDS panel from bone marrow revealed BCR-ABL1 gene fusion in 20% cells.

Discussion: The BCR-ABL fusion gene is a disease-defining clonal abnormality, usually seen in CML and in some cases of ALL, but MDS is rarely associated with BCR-ABL mutation. Patients with MDS seem to have a poorer prognosis with increased transformation to leukemia compared to patients without BCR-ABL mutation. Routine testing for the BCR-ABL translocation is not yet a part of the MDS work up due to its rarity.

Summary: MDS is rarely associated with BCR-ABL1 fusion. Patients have a seemingly poorer prognosis with increased risk of transformation to acute leukemia compared to patients without BCR-ABL1 mutation and are more resistant to conventional chemotherapy.

Introduction

Myelodysplastic Syndrome (MDS) is a group of acquired disorders characterized by ineffective and dysplastic hematopoiesis in the bone marrow with variable risk of progression to acute leukemia. MDS can either be de novo or develop after mutagenic therapy or environmental exposure to toxins, radiation, and chemotherapeutic agent. Symptoms are based on the cell line(s) involved and can present as fatigue, weakness, dizziness, confusion in case of anemia or infections in neutropenia, or bleeding due to thrombocytopenia or dysfunctional platelets. The patients can be risk stratified based on cytopenia(s), cytogenetic abnormalities and medullary blast count.

Philadelphia chromosome is a translocation involving the chromosomes 9 (Abelson Protooncogene: ABL) and 22 (Breakpoint Cluster Region: BCR) with a resultant fusion oncogene which encodes the BCR-ABL protein with constitutive Tyrosine kinase activity. It is a disease-defining entity in Chronic Myeloid Leukemia (CML) and is seen in Acute Lymphoblastic Leukemia (ALL) as well but is rarely reported in patients with MDS, and its presence on prognosis or management is not defined.

We report a case of MDS with the Philadelphia translocation here and reviewed other similar cases.

Case Presentation

A 69-year-old Indian female with a past medical history of hypertension and type 2 diabetes mellites, initially presented with

- Sudden onset of shortness of breath with mild cough
- ST-T changes in anterior lead
- Low blood count with sepsis
- Lower respiratory tract infection

Initially The patient was admitted in Cardiac Intensive Care Unit (ICU) and diagnosed with Acute Coronary Syndrome (ACS) and treatment given accordingly.

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Table 1: FISH for AML with MDS Panel, Interphase/Nuclear in SITU Hybridization [ISCN 2020].

FISH Result: POSITIVE for FISH MDS-EB1				
S.no	**Result (ISCN2020)**	**Chromosome/Color**	**No. of cells**	**Result**
1	nuc ish (CEP 17×2)(TP53×2)	17p13.1 (TP53)-spectrum red 17p11.1-q11.1 (CEP 17)-spectrum green	200 [100%]	Negative
2	nuc ish (3'EVI 1×1.5'EVI1×1)(3'EVI1 con 5' EVI1×2)	3' centromeric sideEVI1-spectrumgreen 5' telomeric side EVI1-spectrum red	20 [10%] 180 [90%]	Positive
3	nuc ish (RUNX1T1×2), (RUNX1×2)	8q22 (RUNX1T1)-Red 21Q22 (runx1)-Green	200 [100%]	Negative
4	nuc ish (DSS23, D5S721×2), (EGR1×2)	5p15.31-15.2 (hTERT)-Green 5q31.2-q32 (CSF1R, EGR1)-Red	200 [100%]	Negative
5	nuc ish (D7Z1×2), (D7S486×2)	7q31 (LSI D7S486)-Red 7p11.1-q11.1 Alpha Satellite DNA (CEP7) Green	200 [100%]	Negative
6	nuc ish (BCR×2), (ABL1×2)/nuc ish (BCR×3)(BCR con ABL1) ×1	9q34 (ABL1)-Green 22q11.2 (BCR)-Red	40 [20%] 160 [80%]	Positive
7	nuc ish (PML×2), (RARα×2)	15q34 (PML)-Red 17q21.1 (RARα)-Green	200 [100%]	Negative
8	nun ish (KMT2A×2)	3'MLL telomeric side-Red 5'MLL centromeric side-Green	200 [100%]	Negative
9	nuc ish (CBFβ×2)	5'CBFβ centromeric-Red 3'CBFβ telomeric-Green	200 [100%]	Negative
10	nuc ish (D8Z2×2)	8p11.1-q11.1 Alpha satellite DNA (CEP8, D8Z2)-Green	200 [100%]	Negative

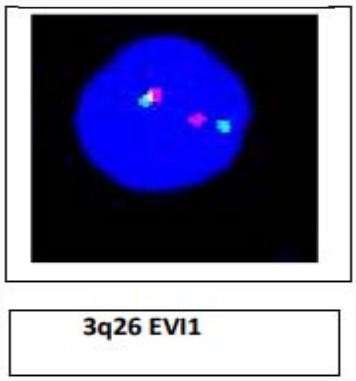

Figure 1: (FISH).

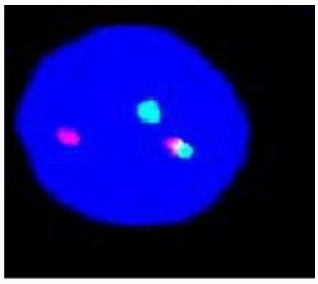

Figure 2: BCR:ABL1 fusion (FISH).

Coronary Artery Angiography (CAG) was done and revealed Double Vessel Coronary Artery Disease (DVCAD), which was non-critical in nature and plan was made to do Percutaneous Transluminal Coronary Angioplasty (PTCA), but was not done.

Bone marrow biopsy was done in view of pancytopenia and suggestive of Myelodysplastic Syndrome (MDS) with Excess Blasts-1 (EB1: 9% blasts in bone marrow).

Bone marrow sample was sent for Fluorescence *in-situ* Hybridization (FISH)-AML and MDS panel. FISH analysis of 200 interphase cells shows presence of rearrangement of the region 3q26 in 10% cells and BCR-ABL1 gene fusion in 20% cells (Table 1 and Figure 1, 2).

The patient was diagnosed as MDS-EB1 with BCR-ABL1 along with ACS with DVCAD (in background) and treated with hypomethylating agent – Azacytidine along with Tyrosine Kinase Inhibitor (TKI) Imatinib. Hospital stay was uneventful.

Discussion

MDS is a clonal process thought to arise from a single transformed hematopoietic progenitor cell [1,2]. The incidence of MDS is variable, but it is estimated to be about 10,000 cases per year in USA, and is usually diagnosed after the age of 50 years [3,4]. Common cytogenetic abnormalities associated with MDS include +8, loss or del of chromosomes 5 or 7, del 20q [5]. The BCR-ABL fusion gene is a disease-defining clonal abnormality, usually seen in CML (in >95% cases) and in some cases of ALL (17% to 25% cases) [6]. MDS is rarely associated with BCR-ABL mutation and is usually reported at the time of progression to acute leukemia [7]. A consensus prevalence of the BCR-ABL fusion gene in patients with MDS is currently unavailable. In the study by Keung et Al, the prevalence seems to be about 2% of cases, but this did not differentiate between *de novo* and treatment-related MDS [8].

The Philadelphia chromosome is formed by the translocation of t(9:22) with a resultant fusion gene which encodes the oncoprotein BCR-ABL1, with enhanced ABL tyrosine kinase activity [9,10], leading to increased proliferation of myeloid cells which could lead to progression of these patients with MDS to acute leukemia.

It is estimated that about a third of MDS cases diagnosed will transform into AML, and the BCR/ABL1 translocation is estimated to be present in approximately 1% of patients with AML [7]. Considering the appearance of the Philadelphia chromosome in patients after or at the time of evolution to leukemia [11-14], it might indicate an overall poorer prognosis.

Overall, patients seem to have a poorer prognosis with increased transformation to leukemia compared to patients without BCR-ABL mutation and do not respond to conventional chemotherapy or supportive care, although they seem to have a semblance of response with the tyrosine kinase inhibitors. These patients also may have increased risk of proliferation and probably transformation into acute leukemia.

Routine testing for the Philadelphia translocation is not a part of

the NCCN recommendations [15], and it is not part of the MDS panel probe testing for molecular genetics and is not listed in the common gene mutations in NCCN, but this translocation can be identified with conventional cytogenetics and when present, treatment with tyrosine kinase inhibitors should be considered.

TKI resistance can occur after treatment with TKIs and checking for Tyrosine kinase domain mutation in these patients is recommended before switching therapy. Furthermore, a national database to study the incidence of these mutations and study of overall survival and prognosis would be helpful in the future.

Summary

MDS is rarely associated with BCR-ABL1 fusion. Patients harboring this cytogenetic abnormality have a seemingly poorer prognosis with increased risk of transformation to acute leukemia compared to patients without BCR-ABL1 mutation and they are more resistant to conventional chemotherapy.

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