A Case Report: *NF*1, *NPM*1 and *IDH1 P*ositive Relapse Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia (AML) is a type of hematological malignancy that affect vital age group from 20-49 years with a broad variety of symptoms including low-grade fever, toothache, easy bruising and life-threatening conditions. This case will be first time in Bangladesh presented with molecular basis and life expectancy of adult AML after chemotherapy

Case Presentation: This study reports a relapse case of AML 38 years Bangladeshi female who presented with weakness, fatigue, fever and gum swelling. She was diagnosed as a case of AML *NPM*1 positive on the basis of peripheral blood finding, bone marrow examination report and immune phenotyping. After relapse, the whole genome sequencing for AML was done and report shows it had other associated genetic *NF1*, *IDH1* and *DNM3T* abnormalities. She got chemotherapy 3+7 induction protocol followed by 3HiDAC consolidation protocol. During relapse time, started azacitidine and vanetoclax therapy. After receiving two cycle, symptom not subsided and died.

Conclusion: Now a days, AML is treated on molecular basis. If the patient of this case, is diagnosed by whole genome sequencing of AML before her chemotherapy her prognosis will be better and life expectancy will increase.

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Introduction

Acute myeloid leukemia (AML) which is a type of hematologic malignancies affect stem cell of blood tissue and consider as the most common acute leukemia in adults. Human being physically and intellectually become manpower for the world at adulthood. As a result, AML breaks the social and familial harmony. According to Hossain et al. (2014) the median age at onset of AML in Bangladesh is 35 years andwas the most frequent haematological malignancy 28.3% cases.[1] AML is an accumulation of leukemic blasts in the bone marrow, peripheral blood, and occasionally in other tissues, with a variable reduction in the production of normal red blood cells, platelets, and mature granulocytes.[2] Familial AML is a rare type of inherited leukemia which is transmitted by a non-sex chromosome in a dominant fashion.[3] Arber stated the revised 4th edition of the WHO classification published in 2017, where AML is classified into 6 categories: AML with recurrent genetic abnormalities; AML with myelodysplasia-related changes (MRC); therapy-related myeloid neoplasms (t-MN); AML, not otherwise specified (NOS); myeloid sarcoma; and myeloid proliferations related to Down syndrome (DS).[4]

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Although a presumptive diagnosis of AML can be made via examination of the peripheral blood smear and bone marrowaspiration (tissue within bone collection is crude procedure but it has no alternate) for identification genetic abnormalities include change in DNA sequence,chromosomal translocations involving transcription factors associated with distinct clinical, morphological, and immunophenotypic features which is required to select plan of management for individual patient. This type of case reported 1st time for Bangladesh and it will encourage our expert physician to take proper steps toward improving management and documentation about AML of Bangladeshi population.

Case Presentation

A 38-year-old female patient from Shahazadpur, Shirajganj, Bangladesh who was admitted October, 2021at Evercare Hospital, Dhaka that presenting with neutropenia associated with anemia and gum swelling with fever. There was no history of any hematological disorder. She had taken covid vaccine 2 weeks before of her AML diagnosis. Her father died by rectal carcinoma and maternal uncle died by lung carcinoma. She had history of medical termination of pregnancy due to huge fetal ascites about 4 months back of diagnosis of AML. She had two healthy child - one male & one female below ten years. On examination, the patient had temperature 101°F, hypothyroid (previously diagnosed and on medication) and no organomegaly in ultrasonography and no cardiac abnormality in echocardiogram.

Physical examination was otherwise unremarkable. The patient had been suffering from toothache, followed by febrile episodes with weakness and fatigue. Morphology and Immunophenotyping of bone marrow were examined by an automated hematologic analyzer (8 color, 3 laser, BD FACS Canto II Becton Dickinson).

Peripheral blood smear examination showed normocytic normochromic red blood cells including few nucleated red blood cells (RBC), white blood cells (WBC) with significant number of blasts that suggestive of acute leukemia. Many giant platelets and platelet aggregates were seen. The differential count of WBC at diagnosis was - neutrophil 0, monocyte 10%, lymphocytes 50%, and myeloid cell 50%. Peripheral blood analyzed according to routine clinical laboratory procedures that showed the leukemic cells myeloid markers were positive for MPO, CD13, CD33, CD 117, CD45, CD38, CD123 and human leukocyte antigen(HLA)-DR and negative for CD14, CD64, CD34, and CD56. The biochemical parameters such as uric acid, bilirubin, creatinine, liver enzymes were normal. Serum LDH was slightly raised. The molecular diagnosis was done (real time PCR) and genetic profile shows only *NPM1* positive (12 exon position) with normal karyotype (NK). Based on this diagnosis and with respect to the patient's severely compromised overall condition, DA 3+7 protocol started. After cytarabine and Daunorubicine-based induction therapy, at day 14 bone marrow sample was collected from iliac bone and study showed - Cd13, CD33, CD34, CD38, CD45, CD117, CD 123 and HLA-DR were positive and 0.01% MRD (minimal residual disease) and *NPM1* were negative. The symptom at diagnosis were subsided but patient developed platelet refractoriness during her chemotherapy. She received 3 HiDAC consolidation therapy. After induction therapy, at day 35 bone marrow was done and showed morphological remission, *NPM1* and MRD were negative. NADIR achieved usually after 19 days of each cycle and followed by giving injection subcutaneously granulocyte colony-stimulating factor (G-CSF).

During her 5th month follow up, in peripheral blood examination reported that RBC was anisocytic anisochromic with 0.58% reticulocyte, neutrophil 27%, monocyte 4.7%.

Bone marrow biopsy showed disease in relapse, blast cell about 26%, myeloid marker positive for CD13,CD15, CD33, CD38, CD45, CD117, CD123, MPO and HLA DR. The genetic profile for AML whole genome sequencing of Leukemia Panel (SNVs, small INDELs and CNVs) by NGS (Next generation sequencing) testing detected mutation in *NPM*1, *IDH*1, *NF*1 and *DNM*T3A. the mutated exon number for *NPM1* was 11 (formerly known as 12), *NF1* at exon 26, *IDH1* at exon 4 and *DNMT3A* exon 20. The azacytidine and venetoclax protocol started. Patient developed septicemia and died during neutropenic stage of 2nd cycle of that protocol.

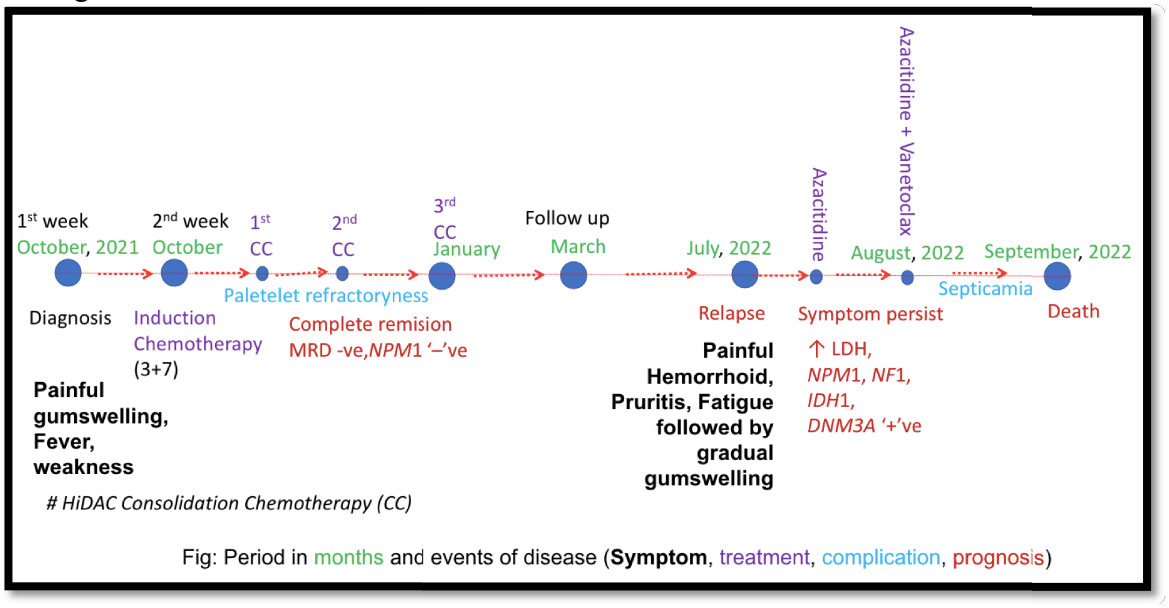

Fig: Period in months and events of disease (**Symptom**, treatment, complication, prognosis)

Discussion

The incidence of acute leukemia is approximately 2.3 per 100000 people per year. On the basis of research, it is known that AML is a low-survival cancer with a 5-year overall survival rate. Initially patient of this case was diagnosed as favorable risk *NPM1* positive AML. As per the European Leukemia Net (ELN) guidelines, *NPM1* mutation in the absence of *FLT3-ITD* is stratified as a favorable risk category. Depending that diagnoses patient was in complete remission after receiving induction therapy. The standard therapy of *NPM*1-mutated AML patients includes "3+7" induction chemotherapy and consolidation therapy.[5] After achieving MRD 0.01%, our case receives 3 HiDAC consolidation therapy. On her 5th months follow up time, she was diagnosed as relapse AML.Rong wong mentioned that *NPM1* represents the most frequently mutated gene approximately 30% in AML and is a good prognostic marker, but some patients ultimately relapse (50%) or fail to respond to therapy.[5] Then started 'Azacitidine + Vanetoclax' drugs before getting NGS report.

The bone marrow aspiration was done and using sample for Whole genome sequencing for AML byLeukemia Panel (SNVs, small INDELs and CNVs) by NGS which showed other mutation *IDH1*, *NF1* and *DNMT3A*in associate with *NPM1* without chromosomal abnormalities.According to Salah Aref et al. that *IDH1* and *IDH2* mutations are negative prognostic markers in AML patients.[6] In addition, *IDH1* mutations showed strong association with *DNMT3A* mutations,*IDH1* mutations were associated with worse survival and lower likelihood of complete remission (CR), especially in patients with *NK*[7] that was very much similar to our case except complete

remission. In one of the recent updates, the US-FDA has approved Ivosidenib (Tibsovo) as a treatment for adult patients with relapsed or refractory IDH1-mutated AML cases. Before getting NGS report, patient of this case finished her 1st cycle ofazacitidine + vanetoclaxprotocol. The symptoms of that appear during relapse, thepainful external hemorrhoid, pruritis on shin skin of both tibia, few gum swealing were persist after that chemotherapy. Ann-Kathrin Eisfeld et al. suggested that *neurofibromin 1* (*NF1*) genebelongs to the 20 most frequently mutated genes in adult AML and has an adverse prognostic impact in patients treated with standard chemotherapy[7].*NF*1 mutations areassociated with lowercomplete remission (CR)rates and shorter overallsurvival in AML patients.[9]The prognostic significance of *NPM1* and *IDH1* or *IDH2* co-mutation in AML is still debatable.The *IDH1* and *IDH2* mutations constitute poor prognostic factors in cytogenetically normal AML with *NPM1* mutation without *FLT3*-ITD.[10] Patients with intermediate-risk AML who had both *NPM1* and *IDH1* or *IDH2* mutations had an improved 3-year rate of overall survival, as compared with patients who had mutant *NPM1* and both wild-type *IDH1* and wild-type *IDH2*.[11] During relapse, the patient develops pruritis on right shin area. According to Li et al. the presence of skin infiltration is often associated with a poor prognosis and short survival time.[12] The patient survives one year after her diagnosis of AML.AML which is not only destroypatient life but it also has impact on social life as well as county economy. The dose of the chemo drug varies on genetic pattern and nation. If the total treatment procedure is under global monitoring system for AML, like the protocol for treatment, it will definitely reduce the treatment related complication, achieve high prognosis, increase survival rate and reduce economic burden and loss of manpower (adult population) and the medical scientist will be able to record response and fate of each case and can update precise treatment procedure like this type of multiple genetic abnormalities.

Conclusion

In present, the chemotherapy and bone marrow transplant for AML is possible in Bangladesh. But the care during ongoing therapy and molecular diagnosis is still challenging in treating AML in Bangladesh. Now a days, adult AML patient is increasing that's why modern facilities and drugs should available in Bangladesh along with need to give special emphasis in record keeping system and should make the nation protocol for Bangladeshi population.

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Conflict of interest

The authors have no conflict of interest.

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