Case Report

Role of ancillary techniques in diagnosis, therapy and prognosis of a case of precursor B-cell acute lymphoblastic leukemia in an elderly patient

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Abstract

The chromosomal abnormality of Philadelphia chromosome is mostly seen in Chronic Myeloid Leukemia (CML). But it is observed that the Philadelphia chromosome (Ph), t(9,22), is the most common cytogenetic abnormality in adult patients with acute lymphoblastic leukemia (ALL), occurring in about 20% to 30 % of all cases. Patients with Ph-positive ALL have breaks in the minor breakpoint region, m—BCR (exons 1—2) lead to a short fusion proteins (p190) and is most frequently associated with Ph chromosome- positive ALL. They have an increased risk for central nervous system (CNS) involvement, an aggressive clinical course and poor prognosis. Historically, they had an inferior outcome when compared with their Ph-negative counterparts. Adult Ph+ patients achieve Complete Remission rates comparable to Ph− ALL patients with standard chemotherapy, but the remissions are short and survival poor. The addition of tyrosine kinase inhibitors (TKIs) including imatinib has dramatically improved outcomes. We are presenting this case report of t(9;22), p190 BCR-ABL1 positive ALL in an elderly female patient of south Gujarat.

Key words

Philadelphia positive, t(9;22), p190BCR-ABL1, Acute lymphoblastic leukemia (ALL), Prognosis, Tyrosine kinase inhibitors (TKIs).

Introduction

The chromosomal abnormality of Philadelphia chromosome is mostly seen in Chronic Myeloid Leukemia (CML). But it is observed that the Philadelphia chromosome (Ph) is the most common cytogenetic abnormality in adult patients with acute lymphoblastic leukemia (ALL), occurring in about 20% to 30% of all cases [1–3]. It results from a reciprocal translocation between the ABL-1 oncogene on the long arm of chromosome 9 and a breakpoint cluster region (BCR) on the long arm of chromosome 22, resulting in a fusion gene, BCR-ABL, that encodes an oncogenic protein with constitutively active tyrosine kinase activity [4].

Genetic profile

The t(9;22) translocation results from fusion of BCR at 22q11.2 and the cytoplasmic tyrosine kinase gene ABL1 at 9q34.1, with production of a BCR-ABL1 fusion protein. In most childhood cases of ALL with t(9;22), ap190 BCR-ABL1 fusion protein is produced. In adults, about half of all cases produce the p210 fusion protein that is characteristic of BCR-ABL1-positive chronic myeloid leukaemia, and the remainder produces the p190 transcript. No definite clinical differences have been attributed to these two gene products. The t(9;22) may be associated with other genetic abnormalities. It is generally believed that the clinical features in such cases are governed by the presence of the t(9; 22).

The incidence of Ph-positive ALL increases with age, and occurs in up to 50% of ALL diagnosed in individuals' ≥50 years old [5, 6]. Patients with Ph-positive ALL have an increased risk for central nervous system (CNS) involvement, an aggressive clinical course and poor prognosis. Historically, they had an inferior outcome when compared with their Ph-negative counterparts [7, 8]. Patients with Ph-positive ALL have breaks in the minor breakpoint region, m—BCR (exons 1—2) lead to a short fusion proteins (p190) and is most frequently associated with Ph chromosome- positive ALL [9]. Cell of origin of B-ALL with BCR-ABL1 is more immature than that of other B-ALL cases [10].

Prognosis and predictive factors

Historically, in both children and adults, B-ALL with BCR-ABL1 has been considered to have the worst prognosis of the major cytogenetic subtypes of ALL. Its higher frequency in adult ALL explains in part the relatively poor outcome of adults with ALL. In children, favorable clinical features including younger age, lower white blood cell count, and response to therapy are associated with somewhat better outcome [11]. Therapy with tyrosine kinase inhibitors has had a significantly favorable effect on outcome [12].We are presenting this case because of its rarity and to report a case of ALL in an elderly female patient of south Gujarat.

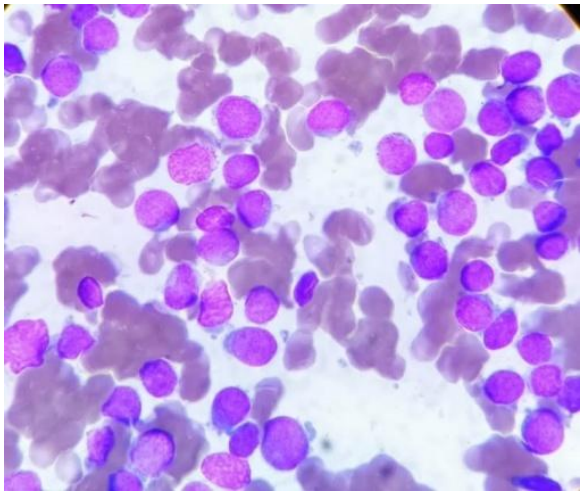
Case report

A 64-years-old female from South part of Gujarat, India presented with complaints of generalized weakness, myalgia, dyspnea on exertion, and loss of appetite for 6 months. All the relevant hematological and biochemical investigations were done and results were as follows: Hemoglobin: 11.5 g%, Total leukocyte count: 18700/cumm, Differential leukocyte count: N-12, L-10, B-1, blasts-53% and myelocyte – 1% Platelets: 37,000/cumm. Bone marrow aspiration showed hypercellular smear comprising 60% blasts which were small to medium in size with round to oval nucleus, coarse chromatin and inconspicuous nucleoli with scanty agranular blue cytoplasm and high N:C ratio. No Auer rods were seen. On light microscopy examination, provisional diagnosis of acute leukemia was made. The patient was advised flow cytometry, cytogenetic and

molecular work-up to confirm diagnosis and categorization.

Photograph - 1 showed Giemsa stained bone marrow aspiration smear with predominately blasts admixed with few lymphocytes in the background of red blood cells. **Photograph – 2** showed Immunophenotyping report suggestive of B-ALL, **Photograph – 3** showed Cytogenetic analysis report confirmed presence of t(9;22), with additional chromosomal anomaly-isochromosome 7 and gain of chromosome 17. **Photograph – 4** showed PCR for the t (9, 22); BCR-ABL fusion genes (p190) are positive. All other investigations including liver function test, serum electrolytes, serum protein, and creatinine were within normal limits. Patients had no significant family history. On clinical examination, the patient was well oriented, afebrile, and normotensive; mild splenomegaly, no lymphadenopathy/ hepatomegaly noted. The patient was diagnosed as BCR-ABL fusion gene-positive precursor B-cell ALL. The patient was put on treatment of chemotherapy. The patient had also received 8 units of platelet-rich plasma and 8 units of packed red blood cells to improve the platelet counts and hemoglobin levels, respectively. The patient is responding well and on follow-up visits, hematological parameters are also improving.

Photograph – 1: Smear showed blast cells with High N:C ratio (40X, Giemsa stain).



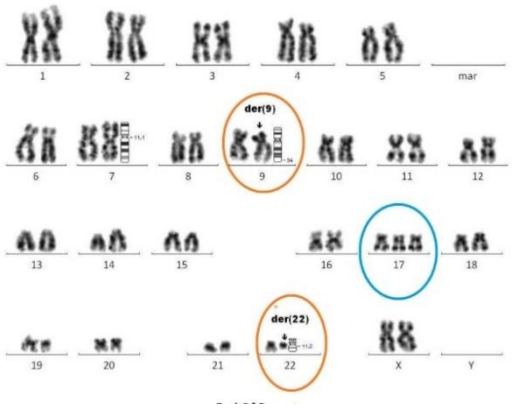
Photograph - 2: Immunophenotyping (Flowcytometry) findings of the bone marrow suggestive of precursor B lineage acute lymphoblastic leukemia (B-ALL).

Result:

Marker	Intensity	Interpretation	Marker	Intensity	Interpretation
Myeloid / Monocytic			B cell		
CD33	Bright	Positive	CD10	Bright	Positive
CD13	-	Negative	CD19	Bright	Positive
CD117	-	Negative	CD22	Moderate	Positive
CD64	-	Negative	CD20	-	Negative
cMPO	-	Negative	cCD79a	Moderate	Positive
Other			T cell		
CD38	Dim	Positive	CD3	-	Negative
HLA DR	Moderate	Positive	CD7	-	Negative
CD34	Moderate	Positive			
CD123	-	Negative			
CD45	Dim	Positive			

Viability: 93%

Photograph – 3: Cytogenetic analysis showed abnormal female chromosome revealed presence of Philadelphia chromosome t(9;22). anisochromosome 7q andd gain of chromosome 17.



Photograph –4: Showed PCR test for detection of BCR-ABL1 p210, p190 and p230 fusion transcripts. p190 transcription positive.

FUSION TRANSCRIPT	RESULT
p190 (e1a2) minor transcript	Detected
p210 major transcript	Not detected
p230 (e19a2) micro transcript	Not detected

INTERPRETATION: Patient sample is found POSITIVE for *BCR-ABL1 (p190)* transcripts.

Discussion

As we all know Ph+ has always been considered as a poor prognostic factor of patients with ALL and is treated with intensive therapy to achieve remission. Available data on ALL in older

patients are relatively meager. In one population-based registry, it was reported that 31% of ALL cases occurred in patients 60 years or older although ALL is most common malignant disease in childhood while it is rare in adults [8]. Here, we had presented a case of 64-year-old female with Ph+ ALL. Majority of patients with B-ALL present with evidence and consequences of bone marrow failure; thrombocytopenia, anemia, and neutropenia. The leukocyte count may be decreased, normal, or markedly elevated. Lymphadenopathy, hepatomegaly and splenomegaly are common. The most prominent symptoms are bone pain and arthralgia [13]. There was mild splenomegaly, no proof of any organ involvement such as hepatomegaly and lymphadenopathy. Neither the patient complained of any bone pain nor arthralgia. The chief complain of our patient were fatigue, mayalgia and pallor. On complete blood count examination, total WBC counts were increased and platelets decreased. In CML, the breakpoint cluster region (BCR) is almost always in the major BCR (M-BCR), spanning exons 12—16 (previously known as b1—b5) and an abnormal fusion protein, p210, is formed, which has increased tyrosine kinase activity. Although breaks in the minor breakpoint region, m—BCR (exons 1—2) lead to a short fusion proteins (p190) and is most frequently associated with Ph chromosome- positive ALL [9]. BCR-ABL1 is relatively more common in adults than in children, accounting for about 25% of adult ALL but only 2–4% of childhood cases [13].

It has a great impact on therapy and prognosis. Adult Ph+ patients achieve Complete Remission rates comparable to Ph− ALL patients with standard chemotherapy, but the remissions are short and survival poor. The addition of tyrosine kinase inhibitors (TKIs) including imatinib has dramatically improved outcomes.

Conclusion

We report this case because of its rarity and also we want to promote greater awareness that cytogenetic & molecular investigations play major role not only in diagnosis but in therapy as well as prognosis. Patients should be thoroughly examined and investigated for proper diagnosis; treatment can be started as early as possible to prevent fatal life-threatening complications. Because of the profound prognostic implication of the Ph chromosome, molecular testing for the BCR-ABL gene rearrangement should be performed for all patients diagnosed with ALL. A polymerase chain reaction (PCR)-based laboratory test is capable of detecting both the p210BCR-ABL and p190BCR-ABL gene transcripts and should be performed in all newly diagnosed patients. Ph− like ALL is now recognized as a distinct entity with prognostic significance. For BCR-ABL–negative B-ALL patients, comprehensive analysis by karyotypic and FISH procedures should be performed.

Pathologist should be very much careful while reporting such entity so that important diagnosis can’t be missed.

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