Philadelphia Chromosome Positive Pre-T Cell Acute Lymphoblastic Leukemia: A Rare Case Report and Short Review

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Abstract Pre-T cell acute lymphoblastic leukemia is a relatively rare leukemia. Twenty to 30 % of adult B cell leukemia cases are Philadelphia chromosome positive and it has a therapeutic and prognostic significance. Incidence and outcome of Ph+ T cell acute lymphoblastic leukemia (T cell ALL) is unknown. Only about 25 cases of de novo Ph+ T cell ALL and 44 cases of Ph+ T ALL in blastic phase of CML has been reported. Differentiation between Ph+ Pre-T ALL/LBL and T cell lymphoblastic crises of chronic myeloid leukemia may be difficult. We report a case of adult T cell ALL having Philadelphia chromosome as the cytogenetic abnormality. He was treated with acute lymphoblastic leukemia induction chemotherapy and Imatinib and achieved complete remission.

Keywords T cell acute lymphoblastic leukemia (T cell ALL) · Philadelphia chromosome positive (Ph+)

Introduction

Twenty to 30 % of all Pre-B acute lymphoblastic leukemia in adults are Philadelphia chromosome positive (Ph+) [1, 2]. This has a prognostic significance as these patients need upfront stem cell transplant in complete remission 1 (CR1)

[3]. Philadelphia positivity in T cell acute lymphoblastic leukemia (T cell ALL) is very rare and only few cases are reported in literature [4–8]. Further, the clinical relevance and prognostic significance of this entity is also not known. T-cell lymphoid blast crises in CML is always a close differential diagnosis with Ph+ T-cell ALL.

Case Report

This 18 year old male presented with complaints of fever, diffuse headache and occasional vomiting for 2 weeks. There was no history of bleeding manifestation, bony pains, swellings in body, blurring of vision, seizures or altered sensorium. On examination he was found to have severe pallor, and generalized lymphadenopathy (maximum lymph node size 2 × 2 cm). There was no evidence of any bleeding manifestation or bony tenderness and examination of oral cavity was normal. Systemic evaluation revealed moderate hepatomegaly (5 cm below right costal margin) and massive splenomegaly (8 cm below left costal margin). There was no testicular enlargement and fundus examination showed mild bilateral papilledema. Baseline hemogram showed marked leucocytosis with anemia and marked thrombocytopenia. Hematological work up and baseline laboratory investigations are given in Table 1.

Patient was started on hydration, alkalization and allopurinol as preventive measures for tumor lysis. Patient was also started on steroids and hydroxyurea for cytoreduction. Leukapheresis was not done due to unavailability of facility at that time. Patient responded well to steroids and his headache and vomiting improved on day-3 of chemotherapy. His counts were 50,000 on day-7 of steroid treatment. He did not develop any features of clinical

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Table 1 Hematological work up and baseline laboratory investigations

Hb (gm/dl)	7.0
TLC (per cmm)	726,000
DLC	Blast 96 %, Neutrophil 2 %, Lymphocytes 2 %
Platelets (/cmm)	35,000
Peripheral smear	Normocytic normochromic RBC, 96 % blasts 2–3 times larger than lymphocytes. Severe thrombocytopenia.
Cytochemistry	PAS-positive, SBB-negative
Serum creatinine (mg/dl)	1.0
Serum potassium (meq/l)	6.0
Serum calcium (mg/dl)	9.2
Serum phosphorus (mg/dl)	5.1
Serum uric acid (mg/dl)	4.2
Serum LDH (IU/l)	1,050
Peripheral blood Immunophenotyping	CD3-79.8 %, CD5-98.9 %, CD7-83.4 %, CD10-46.3 %, CD45-100 %
Bone marrow aspiration	Marrow replaced by blasts constituting 97 %, blasts were CD3, CD10 and TdT positive
CSF examination	Total cell count 10/cmm all lymphocytes, Cytospin-negative for blasts
BCR-ABL by FISH method	94 % cells positive for BCR-ABL translocation
RT-PCR	Positive for <i>e1a2</i> transcript suggestive of p190 protein product
Chest X-ray PA view	Normal
2D-ECHO heart	Normal

tumor lysis syndrome. Patient was started on MCP-841 induction protocol with Imatinib 600 mg/day and weekly triple drug intrathecal therapy. He tolerated chemotherapy well without any episode of febrile neutropenia. By day-15 blasts had cleared from peripheral blood. At the end of induction CSF was normal and bone marrow was in remission. Currently patient is undergoing consolidation chemotherapy.

Discussion

According to WHO classification of acute lymphoblastic leukemia about 70–75 % of adult ALL patients are precursor B-cell acute lymphoblastic leukemia. Adult precursor T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma are relatively uncommon (~25 %) but commoner than pediatric T ALL (~10 %) [1]. Adults with pre B-ALL have Philadelphia positivity up to 20–30 % and this positivity increases with age [2]. Philadelphia positivity is associated with very poor outcomes and these patients need stem cell

transplant in first complete remission (CR1) [3]. Only case reports are there regarding Philadelphia chromosome positive (Ph+) pre T-cell acute lymphoblastic leukemia. Clinical behavior, therapeutic and prognostic significance of this abnormality is currently not known.

A case of Ph+ T cell ALL has been reported in post renal transplant setting as a post transplant lymphoproliferative disorder. This was a 50 year old male who underwent renal transplantation at the age of 45 years for chronic renal failure. He presented with organomegaly and pancytopenia with blasts in peripheral blood. Blasts were positive for T-cell phenotype and cytogenetics revealed Philadelphia chromosome positivity. Patient did not respond to induction chemotherapy and died during induction [4].

Alba Oussama has reported a case of 16 year old boy who had two unusual features, a *bcr-abl* fusion mRNA coding for p210 protein and a T cell immunophenotype. This boy presented with septic shock and pancytopenia likely precipitated by an acute parvovirus B infection. He died 8 months after transplant due to idiopathic pneumonia syndrome [5].

Lim et al. has studied 21 patients of Philadelphia positive *de novo* acute leukemia over a period of 3.5 years. Three of these patients were AML, one patient was biphenotypic and 17 patients were acute lymphoblastic leukemia. Out of these 17 patients only one patient was T-ALL [6].

Tchirkov et al. [7] has reported molecular appearance of *bcr-abl* by RT-PCR based detection method in first relapse in a 5.5 year old boy with T cell ALL. This case report suggested that this molecular abnormality can also appear during the disease course. Coad et al. [8] reported a child with T-cell acute lymphoblastic leukemia (ALL) who at relapse acquired two Philadelphia chromosomes (Ph). Molecular studies at relapse revealed a rearrangement of the major breakpoint cluster region (M-bcr) on chromosome 22.

Barber et al. [9] has studied 280 patients of pre-T ALL/LBL out of which 8 patients had amplification of ABL gene detected by BCR-ABL probe kit by FISH method. This amplification was found to be extrachromosomal as evidenced by metaphase FISH.

Other major confusion among these patients is distinction between Ph+ Pre-T ALL/LBL and T cell lymphoblastic crises of chronic myeloid leukemia [10, 11]. Approximately 44 cases of T cell lymphoblastic crises of CML have been reported in literature. Presence of history of CML (long duration of symptoms, old age, massive splenomegaly, previous diagnosis of CML), presence of increased number of residual circulating granulocytic precursors, eosinophils, and basophils, and presence of major *bcr-abl* breakpoint transcript favors as T cell lymphoblastic crises of CML. None of the CML cases in T-cell lymphoblastic crises showed *bcr-abl* involving the minor breakpoint transcript by RT-PCR. On the other hand

younger age, bone marrow involvement by numerous blasts and presence of minor bcr-abl transcript favors Ph positive Pre-T-ALL.

Our patient is a young adult male who presented with very high leucocyte count and complete replacement of marrow with lymphoid blast without any previous history of chronic myeloid leukemia. He was Philadelphia positive by FISH and also positive for p190 transcript by RT-PCR.

Conclusion

Philadelphia chromosome positive T-cell acute lymphoblastic leukemia is a rare entity. Worldwide limited number of cases have been reported. Clinical relevance, prognostic value and treatment strategy is not well defined for these patients. Differentiation between Ph+ Pre-T ALL/LBL and T cell Lymphoblastic crises of chronic myeloid leukemia may have some clinical and prognostic significance.

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