Original Research Paper

Volume - 11 | Issue - 09 | September - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pediatrics

ADULT TYPE CML IN A CHILD: A RARE PRESENTATION

Dr.sunil Kumar Agarwalla — Asso. Prof. Dept Of Pediatrics, MKCG Medical College, Berhampur, Ganjam, Odisha

Dr.krishna Dash* — Junior Resident,dept Of Pediatrics ,MKCG Medical College,berhampur,ganjam, Odisha. *Corresponding Author

ABSTRACT CML is a clonal myeloproliferative neoplasm of pleuripotent stem cell and consistently associated with BCR-ABL-1 fusion gene located in Philadelphia chromosome. Philadelphia chromosome is the hallmark of CML. There are three phases in CML. CML in children is biologically and clinically different from that of adult type. Management of paediatric CML is difficult as compared with CML in adults, and there is no specific guideline for paediatric CML. Here we are reporting a case with history of repeated blood transfusion within last 6 months diagnosed to have CML.

KEYWORDS : CML, BCR-ABL, Philadelphia chromosome, Myeloproliferative disorder, Imatinib.

INTRODUCTION:

Chronic myeloid leukaemia (CML) is characterized by translocation between chromosomes 9 and 22, resulting in the formation of Philadelphia (Ph) chromosome. Nearly 95% of CML patients shows presence of Philadelphia chromosome in metaphase in cells of myeloid, erythroid and megakaryocytic and lymphoid series.

Breakpoint cluster region (BCR)-ABL1 is generated as the result of this translocation. This BCR-ABL1 messenger RNA results in leukemic cells with growth advantages[1]. CML accounts for only 2-3% of all cases of childhood leukemia.

It is a triphasic disease with most cases (85%) diagnosed in Chronic phase (CP). Symptoms commonly seen in CML are fatigue, fever, sternal tenderness, weight loss, abdominal fullness, bleeding, purpura, splenomegaly. Common blood pictures seen in CML are leucocytosis, anaemia and thrombocytosis[2].Currently tyrosine kinase inhibitors are the mainstay of therapy in CML.

CASE REPORT:

Debashish Kanhar a 4 yr 6 months male child from Phulbani Odisha admitted to MKCG Medical college with chief complain of progressive swelling of abdomen for 6 months and fever for 3 days.

There was history of blood transfusion 4 times within last 6 months. Last blood transfusion was given 1 month back. There was no history of blood transfusion prior to 6 months. No family history of blood transfusion. Child is having one sibling who is doing well.

On Examination child was conscious, oriented, febrile. Pulse rate=112/min regular in rhythm and normal in volume, RR= 20/min regular, SpO2=99% with room air, BP= 90/60 mm Hg in right arm supine position.

Some pallor was there, no icterus or cyanosis or clubbing or lymphadenopathy.

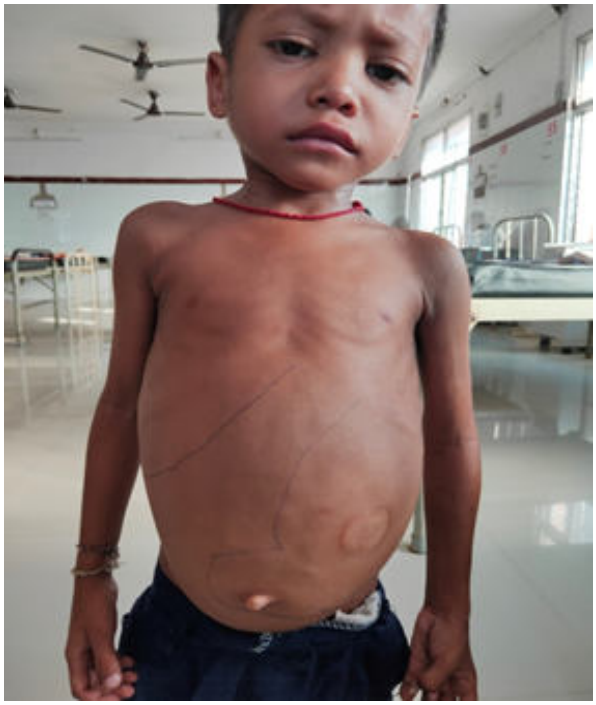
Systemic Examination revealed huge splenomegaly (16cm) below Left costal margin crossing the midline and hepatomegaly of 3cm below the right costal margin. Other systems being in normal limit.

Investigations: TLC=6700/cmm, Hb=7gm/dl, HCT=20.2%, MCV=73.7fl, MCH=25.5pg, MCHC=34.7g/dl, PLT=2.4 lakh/cmm

Neutrophil=34%, Lymphocyte=10%, Monocyte=4%, Eosinophil=1%, Basophil=9%, Reticulocyte count=2%, Myelocyte+ Metamyelocyte=37%, Myeloblast=3%. Impression: Chronic Myeloid Leukemia (Chronic Phase)

Sickling=negative, CXR PA view= No abnormality detected
BONE MARROW EXAMINATION: Erythropoisis suppressed, Myelopoisis accelerated with 3% myeloblast .

Impression: Chronic Myeloid Leukemia (Adult type in Chronic phase



{Photo of child showing abdominal distension with gross splenomegaly}

DISCUSSION:

CML is consistently associated with BCR-ABL1 fusion gene. The chimeric bcr-abl gene is created as the result of transposition of abl gene to breakpoint cluster region of chromosome. CML is a triphasic leukemia. Chronic phase of the disease is characterized by massive leucocytosis. Sudden rise in blast cell and clinical deterioration is seen in Accelerated phase and in Blastic phase(crisis) there occurs rapid deterioration clinically with blasts > 20% in bone marrow. It takes approximately 3-5 years for the progression of CML Chronic phase (CP) to accelerated phase (AP) and blast crisis (BC) [3].

Paediatric CML is rare compared to adult CML. It accounts for approximately 2-3 per cent of cases of newly diagnosed paediatric leukaemia. It is very rare below the age of 1 yr and commonly seen in children older than 12 years[4]. There are significant differences in paediatric and adult CML. Children with CML present with massive splenomegaly, sternal tenderness, fatigue, weight loss, fever hepatomegaly. Biologically, in adult CML, there is a single breakpoint cluster within the first centromeric 1.5 kb of the BCR, whereas in paediatric CML, there is a bimodal breakpoint distribution which is similar to adult Ph+ acute lymphoblastic leukaemia (ALL) with M-BCR rearrangement[5]. Clinical presentation of paediatric CML is

different from adult CML. The median white blood cell (WBC) count at baseline in adult CML ranges from 80 to 150×10^9/l; however, in childhood CML, the median WBC count was 250×10^9/l in a study of 200 patients with a median age of 11.6 years. TLC count data analysis from a study showed that adolescent and young adults have aggressive disease with larger spleen size, lesser haemoglobin and higher blast cells compared with other groups. At three months, higher rate of BCR-ABL transcript level of more than 10 per cent on was seen, although there were no differences in cytogenetic remission, molecular remission and survival with respect to other groups[6].

At present, data in paediatric CML are emerging and there is lack of clear guidelines for paediatric CML. Paediatric patients are susceptible to unique side effects of TKI because of growing age and are also susceptible to long-term toxicities. Due to long life span of paediatric patients, treatment targeting cure appears to be the aim rather than suppression of the disease. Recently, Food and Drug Administration (FDA) approved dasatinib and nilotinib for use in paediatric patients with CML. [7,8]

When to suspect CML in children?

Clinical presentation of splenomegaly with leucocytosis in a child raises the suspicion of CML. Patients usually present with malaise, fatigue, fever, night sweats, weakness and symptoms due to splenomegaly and bleeding because of platelet dysfunction. CML-BC mimics clinical picture of acute leukaemia.

Differential diagnosis

Diseases that can closely mimic CML-CP are leukemoid reaction, juvenile myelomonocytic leukaemia (JMML), atypical CML and other myeloproliferative disorders. Leukemoid reaction is due to infections characterized by high leucocyte count with neutrophilia and left shift. It can be distinguished from CML-CP by the presence of toxic granulations, high leucocyte alkaline phosphatase, lack of myelocyte bulge and focus of infection. Cytogenetic or molecular tests can differentiate it from CML but is not required usually. JMML has a distinct set of diagnostic criteria[9]. JMML is clinically characterized by hepatosplenomegaly, lymphadenopathy, anaemia, fever and skin rash. Ph chromosome is absent in JMML. Atypical CML and other myeloproliferative disorders are rare in children, and these can be distinguished by their diagnostic criteria and absence of Ph chromosome and BCR-ABL1[9]. CML lymphoid BC can be difficult to distinguish from Ph+ ALL. Marked splenomegaly, basophilia, myelocyte bulge and p210 fusion gene (p190 in Ph+ ALL) distinguish CML lymphoid BC with Ph+ ALL. In CML lymphoid BC, Ph chromosome will be in the lymphoblasts and in the neutrophils, whereas in Ph+ ALL, it is restricted to the lymphoid cells[9].

Diagnosis

Peripheral smear shows leucocytosis and differential leucocyte count shows increased number of cells of granulocytic series with peaks in neutrophils, myelocytes and metamyelocytes. Absolute basophilia is seen in all patients and absolute eosinophilia is seen in 90 per cent patients. Absolute lymphocytosis is also commonly seen. Normal TLC does not rule out possibility of CML. Platelet counts are normal or increased in most of the cases. Decreased TPC is seen in <5.5 per cent of patients[10]. Bone marrow aspiration and biopsy shows granulocytic hyperplasia along with maturation pattern similar to peripheral smear. Blasts are <5 per cent of nucleated marrow cells. Dwarf megakaryocytes (smaller megakaryocytes with hypolobulated nuclei) are characteristic findings.

Ph chromosome is the hallmark of CML which can be detected by karyotyping, fluorescent *in situ* hybridization (FISH) and reverse transcriptase (RT)-PCR. In adults, t(9;22) translocation is present in 95 per cent of patients. The remaining five per cent have variant translocations involving a third or even a fourth chromosome in addition to chromosome 9 and 22. In these cases, BCR-ABL1 can be detected by RT-PCR or FISH.

MANAGEMENT

Initiation of treatment Patients are started on allopurinol, oral hydration and hydroxyurea till the diagnosis is established. Despite high leucocyte counts, CML-CP is considered as low-risk for tumour lysis syndrome. Leukapheresis is recommended if patient has priapism, pulmonary infiltrates and severe retinopathy. Imatinib is started after the establishment of diagnosis.

TKIs are the first line of treatment in CML-CP in paediatric CML. Imatinib is currently the standard of care in first line.Imatinib is useful in all phases.It induces complete hematological remission in 90% cases and cytogenic response in 60% cases. Imatinib is available in the strength of 100 and 400 mg. Oral bioavailability is 98.3 per cent with a half life ($t_{1/2}$) of 19.3 h in steady state enabling once daily oral administration[11]. Imatinib due to irritant property is preferably given with a glass of water in sitting position. The recommended dose of imatinib in CML-CP is 260-340 mg/m^2 (maximum absolute dose 400 mg)[12]. Common side effects are Myelosuppression which is usually seen in the first six weeks. Myelosuppression can be due to drug toxicity or disease progression. Imatinib cessation is recommended when neutrophil count is $<1\times10^9$/l and imatinib is restarted when neutrophils $>1\times10^9$/l. Imatinib should be stopped if platelet count is $<50\times10^9$/l; in case of recurrent thrombocytopenia, 20 per cent dose reduction is suggested.In Imatinib resistant cases Dasatinib and Nilotinib can be used.In case of suboptimal response or intolerance to second-generation TKI, patient should be considered for haematopoietic stem cell transplant (HSCT) or enrolled in clinical trials. In case, TKD T315I mutation is detected, either HSCT should be considered or the patient should be enrolled in a clinical trial.

CONCLUSION:

CML is a myeloproliferative neoplasm arising from pleuripotent stem cell associated with BCR -ABL fusion gene located in Philadelphia chromosome.Though it is rare in children it should be thought of in children with massive splenomegaly and repeated blood transfusion. Imatinib is the treatment modality of choice . In case of failure to respond to imatinib dasotinib and nilotinib can be used.

REFERENCE

1. Tanizawa A. Optimal management for pediatric chronic myeloid leukemia: CML in childhood. Pediatr Int. 2016;58:171–9. [PubMed] [Google Scholar]
2. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med. 1999;341:164–72. [PubMed] [Google Scholar]
3. Kantarjian HM, Dixon D, Keating MJ, Talpaz M, Walters RS, McCredie KB, et al. Characteristics of accelerated disease in chronic myelogenous leukemia. Cancer. 1988;61:1441–6. [PubMed] [Google Scholar]
4. Mishra P, Seth T, Mahapatra M, Saxena R. Report of chronic myeloid leukemia in chronic phase from All India Institute of Medical Sciences, 1990-2010. Indian J Med Paediatr Oncol. 2013;34:159–63. [PMC free article] [PubMed] [Google Scholar]
5. Krumbholz M, Karl M, Tauer JT, Thiede C, Rascher W, Suttorp M, et al. Genomic BCR-ABL1 breakpoints in pediatric chronic myeloid leukemia. Genes Chromosomes Cancer. 2012;51:1045–53. [PubMed] [Google Scholar]
6. Kalmanti L, Saussele S, Lauseker M, Müller MC, Dietz CT, Heinrich L, et al. Safety and efficacy of imatinib in CML over a period of 10 years: Data from the randomized CML-study IV. Leukemia. 2015;29:1123–32. [PubMed] [Google Scholar]
7. U.S. Food & Drug Administration. FDA approves dasatinib for pediatric patients with CML. [accessed on February 18, 2019]. Available from: http:// www. fda. gov/ drugs/ resources-information-approved-drugs/fda-approvesdasatinib-pediatric-patients-cml .
8. U.S. Food & Drug Administration. FDA approves nilotinib for pediatric patients with newly diagnosed or resistant/intolerant Ph+ CML in chronic phase. [accessed on February 18, 2019]. Available from: https:// www. fda. gov/ drugs/ information on drugs/ approved drugs/ ucm602264.htm .
9. Aber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405. [PubMed] [Google Scholar]
10. Anastasi J, Feng J, Dickstein JI, Le Beau MM, Rubin CM, Larson RA, et al. Lineage involvement by BCR/ABL in Ph+ lymphoblastic leukemias: Chronic myelogenous leukemia presenting in lymphoid blast vs.Ph+ acute lymphoblastic leukemia. Leukemia. 1996;10:795–802. [PubMed] [Google Scholar]
11. Thiele J, Kvasnicka HM, Schmitt-Graeff A, Zirbes TK, Birnbaum F, Kressmann C, et al. Bone marrow features and clinical findings in chronic myeloid leukemia – A comparative, multicenter, immunohistological and morphometric study on 614 patients. Leuk Lymphoma. 2000;36:295–308. [PubMed] [Google Scholar]
12. Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. ClinPharmacokinet. 2005;44:879–94. [PubMed] [Google Scholar]