CASE REPORT

Philadelphia positive chronic myeloid leukemia mimicking acute lymphoblastic leukemia in a child

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ABSTRACT

Chronic myeloid leukemia (CML) is a rare hematological malignancy in children. The more common acute lymphoblastic leukemia (ALL) needs to be excluded in cases with lymphoid blast crisis phase of childhood CML. A 12-year-male child with generalized lymphadenopathy and hepatosplenomegaly had a crisis phase of presentation instead of the usual chronic phase of onset of disease. Hematological tests and molecular study were performed. Peripheral blood, bone marrow and lymph node fine-needle aspiration cytology smear showed features of CML in blast crisis. Blast cells were myeloperoxidase negative. Philadelphia chromosome with major BCR-ABL fusion product and B-cell lineage immunomarkers indicated CML origin of blasts rather than *de novo* ALL. Usually myeloid blast crisis is common in CML but the present case had lymphoid blast crisis which is less commonly documented. We report a case of 'adult form of CML in the juvenile age group with lymphoid blast crisis and extramedullary blast proliferation.'

Key words: ALL, blast crisis, CML, Ph chromosome, quantitative PCR

INTRODUCTION

Chronic myeloid leukemia (CML) is the classic chronic myeloproliferative disorder with a molecular genetic evidence of characteristic Philadelphia chromosome.[1] CML commonly affects middle aged to elderly persons and less commonly seen in children and constitutes less than 3% of pediatric and adolescent leukemias.[2] Two types of CML are seen in childhood age group: (1) two-third are adult form of CML seen in adolescents and (2) the rest one-third are juvenile form of CML seen in children below 2 years of age. CML have multiple phases in sequence: chronic, accelerated and blastic phases.[3] A 12-year-old male child in CML with Philadelphia chromosome positive (Ph +ve) presented in blast crisis. Authors have reported a similar case of 12 year Pakistani boy with TdT activity only without any B- or T-lymphoid markers.[4] As TdT may be expressed in both myeloblasts and lymphoblasts, so we confirmed further the specific lineage of blast crisis with a panel of immunomarkers by flow cytometry. The blast crisis presentation and cytochemical evidence of lymphoid blast carries a worse prognosis led us to exclude acute lymphoblastic leukemia (ALL) by ancillary tests as it is the predominant leukemia in childhood with favorable outcome. In lymphoid blast crisis of CML, quantitative PCR detects expression of Mbcr-type transcript with no evidence of Mbcr-type.[5] Quantitative PCR precisely indicated the case as 'adult form of CML in lymphoid blast crisis'. About 95% of pediatric CML present in chronic phase.[6] This type of blast crisis at presentation accounts for 10% of cases of CML and may mimic ALL morphologically if it is a childhood presentation.

CASE REPORT

A 12-year-male child was admitted in our hospital with severe pallor, weakness, loss of weight, fever, abdominal pain and

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distension of 15 days duration who was apparently alright before that period. The boy belonged to low socioeconomic status and he had taken some antipyretics and multivitamins for fever and weakness in outpatient department of a remote village dispensary. On physical examination, he had huge splenomegaly and hepatomegaly, sternal tenderness and generalized lymphadenopathy. The hemogram showed Hb 6.2gm%, total leukocyte count of 360x 10^9/L, total platelet count of 40x10^9/L, differential count: neutrophils 2%, basophils 2%, myelocytes 3%, blasts 93%. In peripheral smear, the RBC series showed severe degree of hypochromia with mild degree of anisopoikilocytosis and occasional normoblasts. WBC series showed marked leukocytosis predominantly blasts along with few basophilic myelocytes and basophils. Platelet series showed thrombocytopenia. The impression was CML of adult type with blast crisis [Figure 1]. Fetal hemoglobin level was within normal range. Leukocyte alkaline phosphatase (LAP) score was increased. Bone marrow smear was markedly hypercellular with markedly decreased fat cells. Erythropoiesis was severely depressed and normoblastic. Myelopoiesis was markedly depressed and replaced by blast cells which were large cells with high n/c ratio, coarse chromatin, 1-2 nucleoli, scanty pale basophilic cytoplasm without granules constituting more than 90% of marrow nucleated cells along with few basophils. Some basophilic myelocytes were also seen [Figure 2]. Myeloperoxidase stain showed negativity in blast cells [Figure 3]. Bone marrow smear impression was CML more likely in lymphoid blast crisis. Some myeloid blasts may be MPO –ve. So to reach at a conclusive diagnosis of lymphoid lineage of blasts, flow cytometry (FCM) was done. As the patient had generalized lymphadenopathy, each of the lymph nodes measuring around 1 cm, fine-needle aspiration cytology (FNAC) of cervical lymph node was done and smear showed same cytologic picture as in peripheral blood and bone marrow smears [Figure 4]. Blastic phase of CML has symptoms of fever, weight loss, refractory splenomegaly and lymphadenopathy along with the hematological features of blasts more than equal to 20%, extramedullary blast

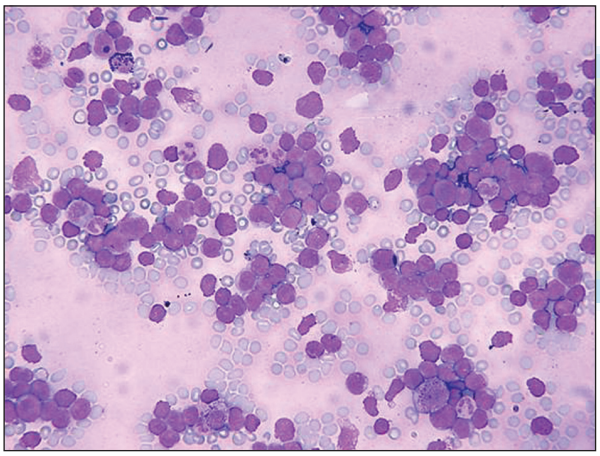

Figure 1: Peripheral blood smear: numerous blasts, few basophils, a basophilic myelocyte, neutrophils and few normoblasts (Leishman stain ×400)

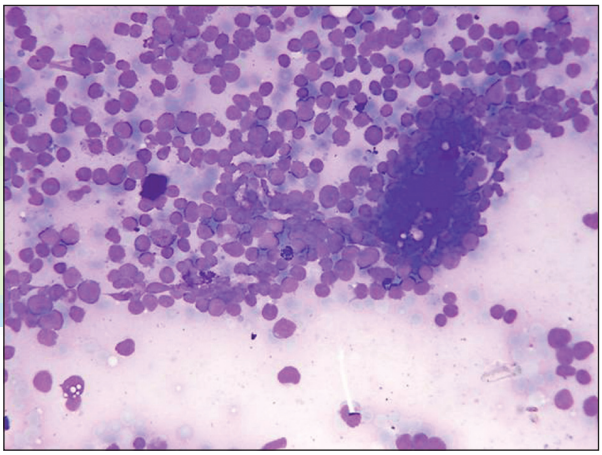

Figure 2: Bone marrow smear: bone marrow fragments, blasts in clusters, few basophils and a basophilic myelocyte (Leishman stain ×400)

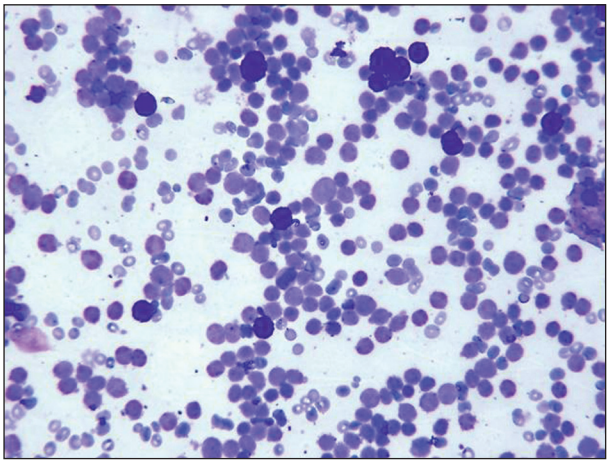

Figure 3: Myeloperoxidase stain of bone marrow; blasts negative; myeloid cells positive (MPO ×400)

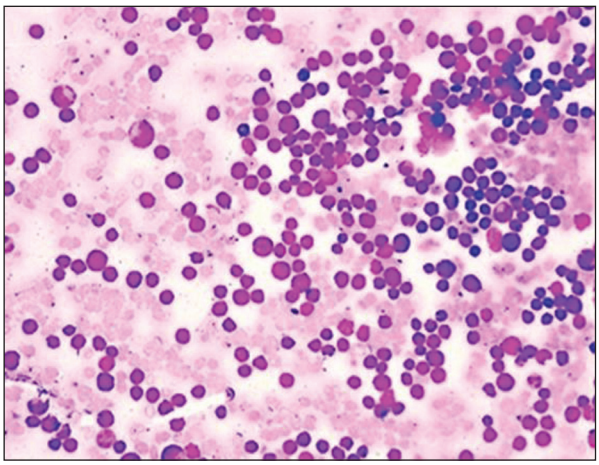

Figure 4: Cytoaspirate smear: sheets of blasts along with basophils, myelocytes and reactive lymphoid cells on a hemorrhagic background (hematoxylin and eosin stain ×100)

proliferation, large aggregates or clusters of blasts in the bone marrow and the diagnosis is made when one or more of the listed features are present.[7] We collected the blood and bone marrow aspirate samples along with lymph node aspirates in EDTA vials along with smears of peripheral blood, bone marrow and lymph node aspirate. All those samples along with detailed clinical information and the diagnosis made at our end were subjected for ancillary studies. Ph chromosome study was done by conventional cytogenetic study, quantitative RT-PCR to detect the length product corresponding to chimeric BCR-ABL protein and immunophenotyping by flow cytometry. The karyotypic analysis detected Ph chromosome with t (9;22)(q34;q11). The BCR-ABL gene rearrangement by quantitative PCR (RT- PCR) was 72.59% and the type of translocation was M-BCR (Major BCR) confirmed CML. Depending on the position of BCR breakpoint, various BCR-ABL fusion products are translated into proteins. The overwhelming majority of CML cases result from a b2a2 or b3a2 fusion leading to the formation of a p210-kd form of BCR-ABL protein corresponding to Major BCR whereas in ALL p190-kd protein product Minor BCR is formed.[8] Quantitative RT-PCR was done to determine the size of the gene product in order to exclude *de novo* ALL from CML. Immunophenotyping was performed by flow cytometric analysis using a flow cytometer. Samples were processed by using standard techniques.[9] Cells initially were gated for analysis by using CD45 versus side scatter; accordingly the gating strategy was followed. It was evaluated by using a panel of monoclonal antibodies, which included precursor B- and T-cell marker, terminal deoxynucleotidyl transferase (TdT) followed by the precursor B-cell cytoplasmic CD22 (CDc22). After subjecting MPO-negative blasts to flow cytometry, the lineage was finally established to be precursor B-lymphoid blast cells positive for CDc22 markers. CD45-gated plots show positivity for TdT and cytoplasmic CD22. The blast cells were CD45 positive (91.87%), TdT positive (89.25%) and CDc22 positive (42.38%). The blasts were CD45+ve, TdT+ve and Cytoplasmic CD22. CD45 is +ve for all lymphoid cells (i.e. lineage independent). TdT is normally expressed in both early pre-B and T-lymphoid cells and also in AML. Cytoplasmic CD22 is a B-cell lineage-specific antigen expressed virtually in all cases of precursor B-lymphoid cells only.[10] This patient died due to pneumonia and septicemia within 2 weeks of diagnosis though chemotherapy regimen was immediately started. In blastic phase, the presence of more than 50% blast cells in the blood has been identified as independent predictors of worse survival and the blast cells constituted 93% of marrow nucleated cells in bone marrow smear in the present case.

DISCUSSION

We arrived at a precise diagnosis of 'adult form of CML with lymphoid blast crisis in juvenile age group with extramedullary blast proliferation' after interpretation of morphology, cytochemical stain, cytogenetic study and immunophenotyping. Our case of a 12-year male child is in 'adult form' of CML in the juvenile age group because he is Philadelphia (Ph) positive and fetal hemoglobin (HbF) negative in the adolescent age group without myelomonocytic cell proliferation. 'Juvenile form' of CML also presents in the pediatric age group but are Ph negative and HbF positive with excessive myelomonocytic proliferation.

The blasts were morphologically lymphoblast rather than the more conventional myeloblast seen in one-third of cases. Although Ph chromosome is hallmark of CML, it is not exclusive to CML. 2-5% of childhood ALL are Ph+ve. Moreover, we found basophils and basophilic myelocytes in the peripheral blood smear and in lymph node aspirate smear which is unusual of ALL. Blastic phase is usually associated with severe bacterial infection. Thus, blast crisis is considered as the obvious cause of death in CML. Two features states rarity of our case. Firstly, it presented with blast crisis. Secondly, this CML has a childhood presentation, the median age group of CML cases being 53 years and constitutes less than 5% of all childhood leukaemia.

The morphologic presence of basophils and basophilic myelocytes and also in FNAC, MPO-negative stain, Ph chromosome, quantitative PCR (Major BCR) and precursor B-cell lineage by immunomarkers in FCM played a well-established role in diagnosing the case precisely as CML with lymphoid blast crisis. Thus, the more common possibility of ALL in this child was categorically excluded. CML in blast crisis presentation in children is extremely rare.

Homozygous deletion of p16 tumor suppressor gene is associated with lymphoid transformation of CML, but such deletions are not seen in the chronic phase and in myeloid blast crisis.[11] Of course , there still exist challenges to management in such cases. Further research into the biology of aggressive phase of CML is required to develop novel targets to improve outcomes.

REFERENCES

1. Soh BN, Klein F, Feldhahn N, Muschen M. B-lymphoid or myeloid lineage identity of cell lines derived from chronic myeloid leukemia blast crisis. Cancer Genet Cytogenet 2005;16:187-8.
2. Iyer P, Carey P, Brown N, Samarasinghe S. Pediatric chronic myeloid leukemia with B- cell lymphoid blast crisis at presentation. Blood Res 2013;48:151-2.

3. Calabretta B, Perrotti D. The biology of CML blast crisis. Blood 2004;103:4010-22.
4. Hann IM, Gorst DW, Jones PM, Evans DI. Chronic myeloid leukaemia in a child. A closely observed case. Arch Dis Child 1978;53:252-4.
5. Suryanarayan K, Hunger SP, Kohler S, Carroll AJ, Crist W, Link MP, *et al*. Consistent involvement of bcr gene by 9;22 breakpoints in pediatric acute leukemias. Blood 1991;77:324-30.
6. Millot F, Traore P, Guilhot J, Nelken B, Leblanc T, Leverger G, *et al*. Clinical and biologic features at diagnosis in 40 children with Chronic myeloid leukaemia. Pediatrics 2005;116:140-3.
7. Vardiman JW, Harris NL, Brunning RD. World Health Organisation (WHO) Classification of myeloid neoplasms. Blood 2002;100:2292-302.
8. Kareen K, Reichard KK. Chronic myeloid leukemia. In: Greer JP, editor. Wintrobe's clinical hematology. 12th ed. Vol. 2, Philadelphia: Lippincott Williams and Wilkins; 2009. p. 2006-30.
9. Reley RS, Massey D, Jackson-Cook C, Idowu M, Romagnoli G. Immunophenotypic analysis of acute lymphocytic leukemia. Haematol Oncol Clin N Am 2002;16:245-99.
10. Head DR. Diagnosis and classification of the acute leukemias and myelodysplastic syndrome. In: Greer JP, editor. Wintrobe's clinical hematology. 12th ed. Vol. 2, Philadelphia: Lippincott Williams and Wilkins; 2009. p. 1808-19.
11. Sill H, Goldman JM, Cross NC. Homozygous deletions of the p16 tumour suppressor gene are associated with lymphoid transformation of chronic myeloid leukemia. Blood 1995;85:2013-16.

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