

Lymphoid Blast Crisis in a Case of Paediatric Chronic Myeloid Leukaemia: An Unusual Presentation of An Uncommon Malignancy

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ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm in which the granulocytes are the major proliferative component and is characterised by the chromosomal translocation t(9;22)(q34.1;q11.2) leading to the formation of Philadelphia chromosome (Ph) containing the BCR-ABL1 fusion gene. This entity is quite rare in paediatric age group and even unusual is a child presenting for the first time in an accelerated or blast crisis. Here we unfold an noteworthy case of a 9 year old school going child presenting with complains of vague abdominal distension who on further evaluation was found to be living through leukaemia.

Keywords: Acute Leukaemia; Blast Crisis; Paediatric Chronic Myeloid Leukaemia; Splenomegaly

Introduction

World Health Organization (WHO) defines CML as a myeloproliferative neoplasm in which the granulocytes are the major proliferative component and which is invariably characterized by the chromosomal translocation t(9;22)(q34.1;q11.2) leading to the formation of Philadelphia chromosome (Ph) containing the BCR-ABL1 fusion gene. [1] The disease mainly affects older adults and amongst men with an age adjusted incidence of 18 per million per year which further shrinks down to less than 1 per million per year in children and adolescents less than 20 years of age. [2,3]

We here present a fascinating case of a 9 year old child who presented for the first time at our medical setup as a case of CML in blast crisis.

Case Report

A 9 years old male child, 1st product of a non-consanguineous marriage presented to the paediatrics clinic with complains of anorexia of two months duration and abdominal distension as noted by his mother for past eight days. Clinically he was febrile (100.4°F) and pale with generalized lymphadenopathy (cervical, axillary and inguinal group). Liver was palpable 2cm below the right subcostal margin while spleen was palpable 24 cm below the left subcostal margin extending till right iliac fossa (Hackett's Grade 5 splenomegaly).

With a working diagnosis of Massive Splenomegaly and a differential diagnosis of Myeloproliferative Neoplasm v/s Hyper-reactive malarial spleen v/s Kala Azar, further investigations were planned. His initial blood evaluation revealed normocytic normochromic anaemia with a raised total leukocyte count (TLC) and thrombocytopenia. TLC was 2,39,000/mm³ with a differential count of blasts-25%, myelocytes-17%, metamyelocytes-12%, neutrophils & band forms-26%, lymphocytes -10%, monocytes-2%, eosinophils-5% and basophils-3% (Figure 1A). The blasts were negative for myeloperoxidase (MPO) cytochemistry. With a further refinement in diagnosis (MPO negative Acute Leukaemia), bone marrow evaluation was planned keeping in mind immunophenotyping and cytogenetics. In view of left shift in myeloid series, presence of basophils and clinical history of massive splenomegaly a possibility of CML in blast crisis was also suggested.

Bone marrow aspirate revealed 72% blasts having high nucleo-cytoplasmic (N:C) ratio, scant basophilic agranular cytoplasm, open nuclear chromatin and 1-2 prominent nucleoli (Figure 1B). No Auer rods were visualised in the blasts and these blasts were MPO negative (Figure 1C). Bone marrow biopsy revealed 100% cellularity with replacement of the marrow spaces by blasts having similar cytomorphology (Figure 2A&B). Grade II marrow fibrosis was evident (Figure 2C). On immunohistochemistry (IHC), the blasts were positive for CD34, CD79a, CD19 and CD10 while were negative for MPO, CD117 and CD3 (Figure 3).

Immunophenotyping (Figure 4) on peripheral blood revealed 30% blasts population which was gated using CD45/SSC and FSC/SSC strategies and these blasts expressed dim CD45, moderate HLA-DR, CD19, CD20, CD79a, CD10, CD34 and CD38 while they were negative for CD13, CD117, CD56, CD2, cCD3, CD5, CD7, MPO, CD14, CD15, CD33, CD64 and CD36. So a final impression was of common acute lymphoblastic leukaemia antigen (CALLA) positive B-lymphoblastic leukaemia (pre-B ALL).

Interphase fluorescence in situ hybridisation (FISH) on peripheral blood using dual colour dual fusion probe showed BCR-ABL1 fusion positivity in 98% of cells (196/200 cells). Occasional myeloid cells present in the smears studied also showed BCR-ABL1 positivity, thus favouring a diagnosis of CML in lymphoid blast crisis.

During the course of hospital stay, the child developed central nervous system (CNS) involvement in which cerebrospinal fluid (CSF) cytology revealed occasional blasts along with myeloid cells. Child was started on triple intrathecal regime of cyclophosphamide-dexamethasone-methotrexate in addition to Dasatinib, Prednisolone, Allopurinol and Folic acid. Subsequent CSF cytology was negative for blasts. The child was put on Berlin-Frankfurt-Munster (BFM) protocol for ALL along with Dasatinib later. Follow up blood investigations revealed a decreasing trend in the blast count. He had a complete haematological response in the sense that splenomegaly regressed completely; TLC was 4,430/mm³ with no circulating immature myeloid forms or basophils. At present, he is being worked up for allogeneic stem cells transplant and a suitable donor match is being looked in.

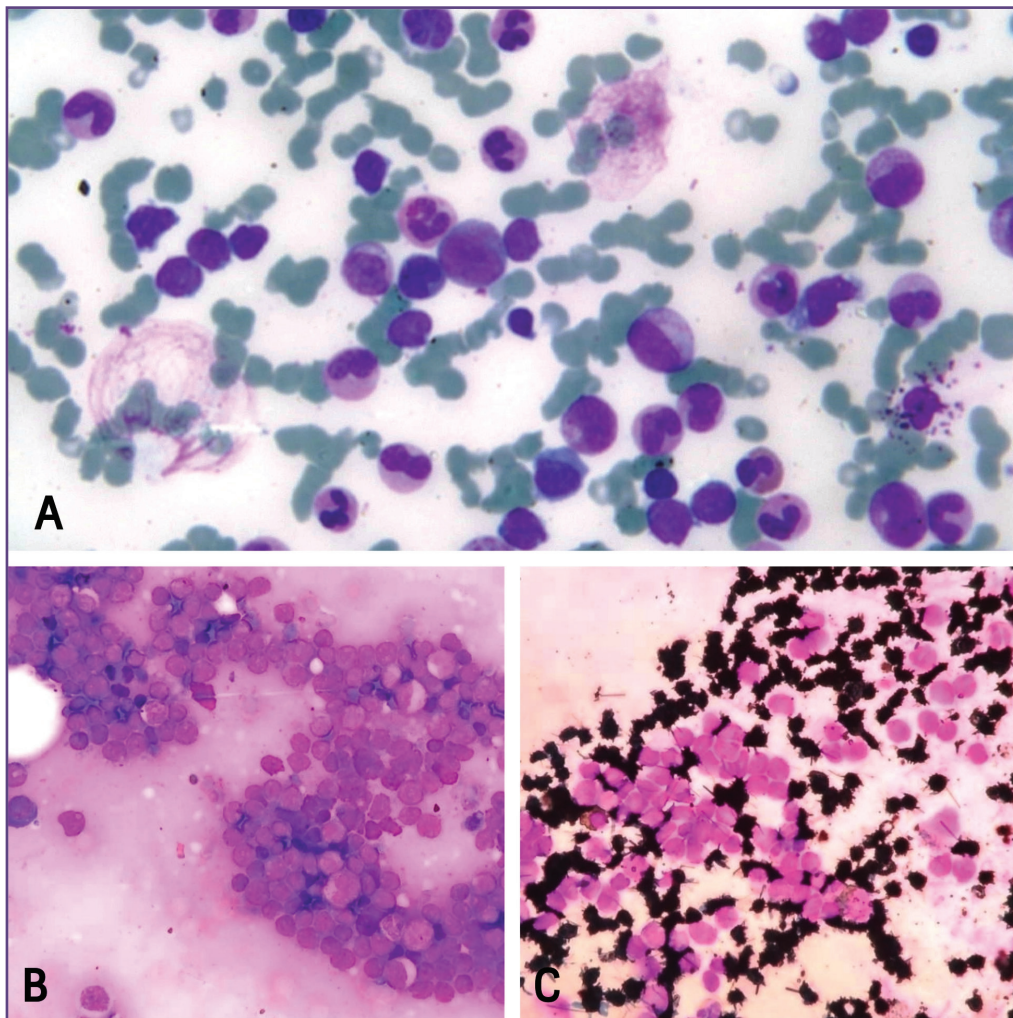


Fig. 1: A - PBS showing marked leukocytosis with numerous myelocytes, metamyelocytes and mature neutrophils along with increased blasts. (Wright's Stain; 400x); B - Bone marrow imprint showing increased blasts (Wright's stain; 100x); C - Blasts are negative for myeloperoxidase cytochemical staining (100x).

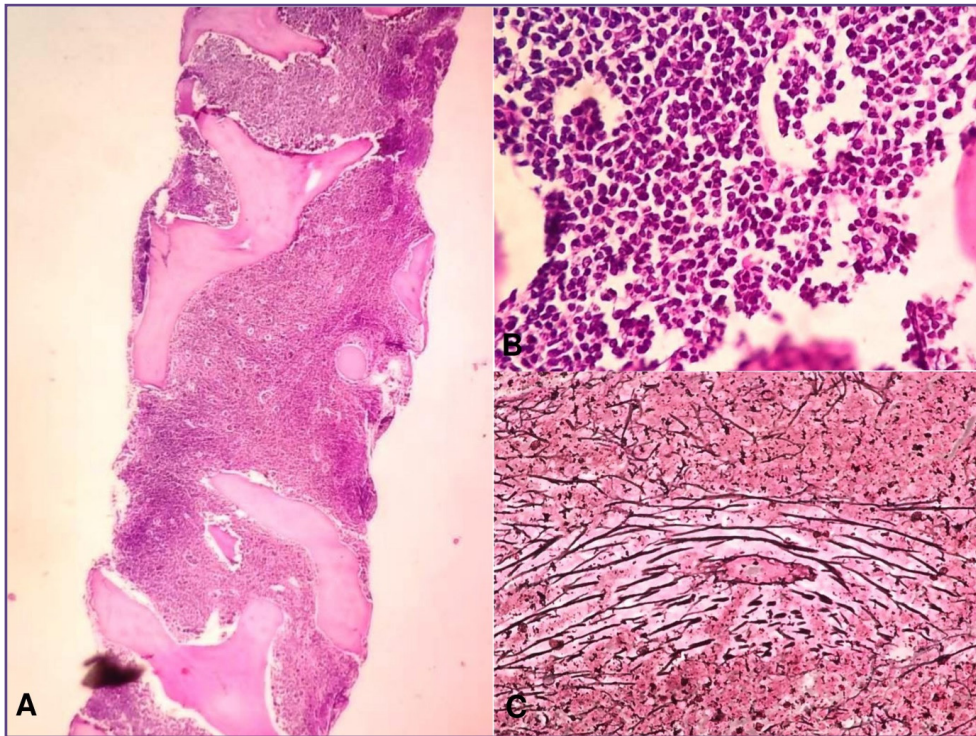


Fig. 2: A - Hypercellular bone marrow with almost 100% cellularity (H&E stain; 40x); B - Marrow space completely replaced by blasts (H&E stain; 400x); C - Diffuse and dense increase in reticulin fibres with frequent intersections (Grade II Marrow Fibrosis) (Reticulin Stain; 400x).

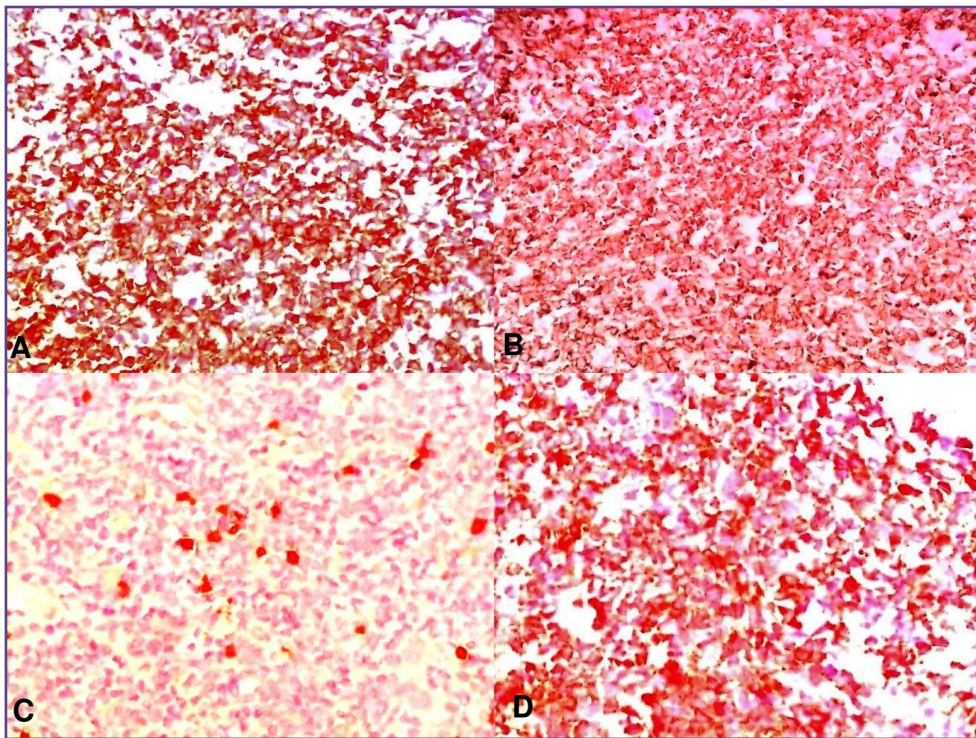


Fig. 3: The blasts are positive for CD34 (A), CD10 (B) and CD19 (D), while they are negative for CD3 (C). Blasts were also negative for MPO and CD117.

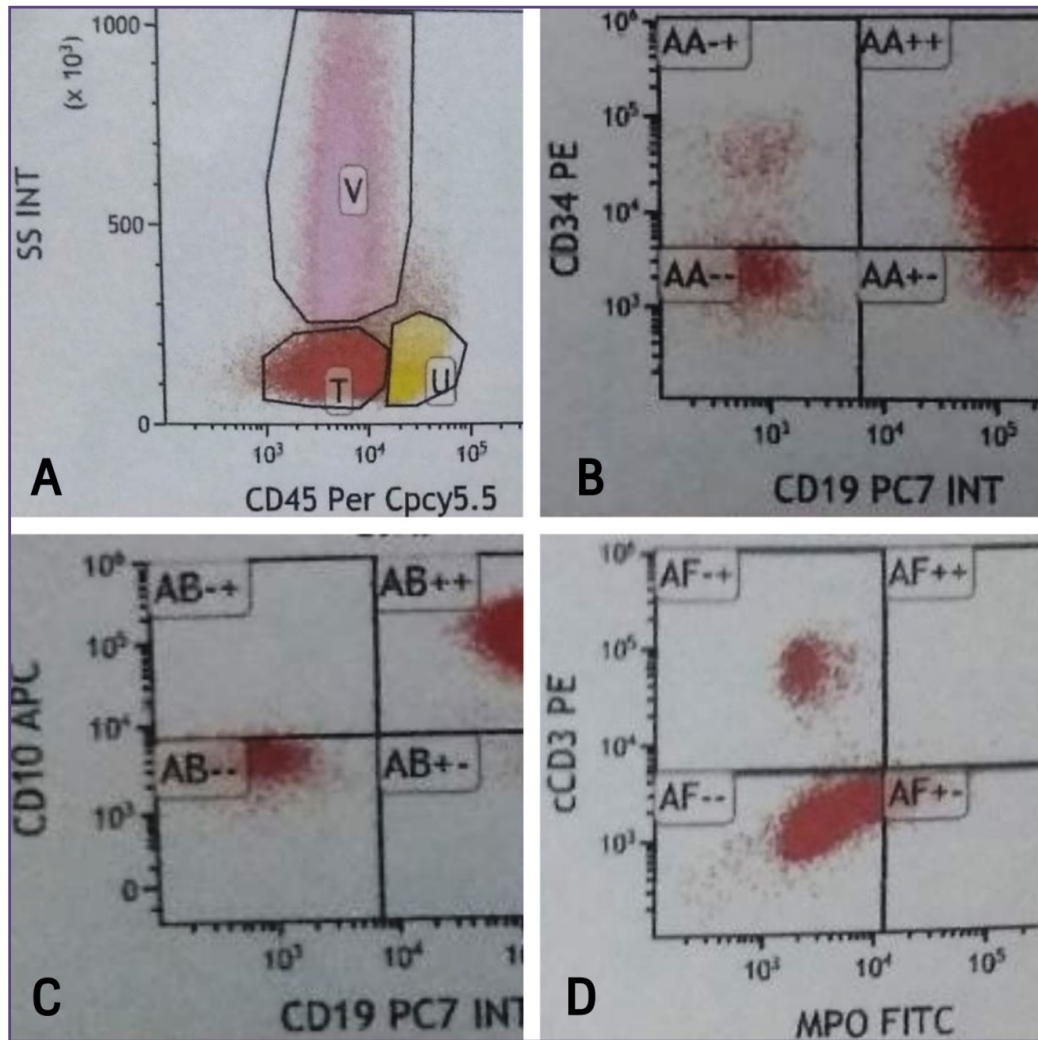


Fig. 4: CD45 v/s Side Scatter plot shows blasts to be dim positive for CD45 (A). The blasts are positive for CD34, CD19 and CD10 (B,C), while are negative for MPO and cytoplasmic CD3 (D).

Discussion

CML is a rare myeloproliferative neoplasm and usually occurs in middle aged adults. Its incidence dips down drastically in the paediatric age group to the tune that only few studies are available regarding this. Most of the patients present in chronic phase (CP) like in adults. They do progress to accelerated phase (AP), if left untreated and finally to blast phase (BP) / blast crisis. So, the disease follows a tri-phasic pattern. Literature analysed gives a rough estimate of around 5% of paediatric CMLs presenting in either AP or BP.^[4]

There is a list of defining criteria for AP of CML as laid down by WHO.^[1] BP of CML is defined by WHO as $\geq 20\%$ blasts in peripheral blood and/or bone marrow or the presence of extramedullary proliferation of blasts. In majority of the patients who present in BP, the blast lineage

is myeloid which may include neutrophilic, monocytic, eosinophilic, basophilic, erythroid or megakaryocytic blasts. In a lesser group of cases, the blasts are lymphoid in nature predominantly of B-cell origin, even though T-cell and Natural Killer (NK) cell origin may also be seen in rare circumstances. In less than 5% of CML cases presenting in BP, the blast lineage can be of mixed phenotype.

In our case, the child presented as acute leukaemia and in the absence of documented CML-CP, it is extremely difficult to segregate between BCR-ABL1 positive ALL and lymphoid blast crisis of CML. BCR-ABL1 positive ALL is a proven entity and accounts for around 2-4% cases of paediatric ALL and is more common in adults.^[5] But some definite strong indicators of lymphoid blast crisis include a massive splenomegaly, predominance of metamyelocytes and myelocytes in peripheral blood and or

bone marrow (myeloid bulge), concurrent basophilia and a p210 BCR-ABL1 transcript. In our case, the child had massive splenomegaly and myeloid bulge on peripheral blood evaluation. The child had basophils in the range of 3-4% at presentation and breakpoint cluster region was not evaluated for this child. So with this overall picture, it is safe to assume that the child had presented as a case of lymphoid blast crisis of CML.

Conclusion

The progression of a case of CML-CP to AP and BP is well known historically in adults, which have come down drastically with the effective use of tyrosine kinase inhibitors (TKIs). But in the present day scenario presentation in blast crisis of CML is rare occurrence in an adult, let alone a child. However, one should have a strong index of suspicion with the overall clinical and haematological picture as novel drugs are being introduced after research into the molecular biology of various phases of CML.

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