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Case Report

Pediatric CML Presenting in Blast Crisis- A Rare Occurrence; Report of 3 Cases and Review of Literature

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Abstract

Pediatric CML's as such is a rare entity and pediatric CML's presenting with blast crisis at initial presentation is even rarer. We report 3 cases of pediatric CML in blast crisis at initial presentation.

ABBREVIATIONS

CML: Chronic Myeloid Leukemia; CP: Chronic Phase; AP: Accelerated Phase; BC: Blast Crisis; OPD: Outpatient Department; TLC: Total Leucocyte Count; Hb: Hemoglobin; MPO: Myeloperoxidase Stain; BM: Bone marrow Examination; FCM: Flow Cytometry; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; M-BCR-ABL1- Major-BCR-ABL1; PAS: Periodic Acid Schiff Stain; IHC: Immunohistochemistry; WBC: White Blood Cell; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; MPAL: Mixed Phenotypic Acute Leukemia; MPAL/NOS: Mixed Phenotypic Acute Leukemia/Not Otherwise Specified; FISH: Fluorescent *In Situ* Hybridization; ASCT: Allogenic Stem Cell Transplant; TKI- Tyrosine Kinase Inhibitors

INTRODUCTION

Chronic myeloid leukemia constitutes around 3% of all leukemia's in children and adolescent age group below 20 years. It has an annual incidence of 1 in 1,000,000 [1] in pediatric population. In contrast, CML comprises 15% of all adult leukemias [2]. It has a triphasic course consisting of chronic phase, accelerated phase and blast crisis. Most of these patients present in chronic phase and slowly progress if left untreated. A small number of patients may present directly in blast crisis.

Exact incidence of BC at presentation in pediatric patient remains unknown. Extensive literature search revealed a 5% incidence in children who may directly present either in AP or BC [3]. However surprisingly, in a span of one year we received a total of 4 cases of pediatric CML of which 3 (75%) presented in blast crisis which is an unusually high incidence. The clinical presentation and investigations for all the 3 cases are given in Table (1).

CASE PRESENTATION

Case 1

A 4-year-old female child presented to medicine OPD with complaints of fatigue, myalgia and abdominal pain for 3 weeks. On examination there was pallor, and splenomegaly (2 cm below costal margin). Laboratory investigations revealed leucocytosis with TLC- 580x10^9/L, Hb-14.2 g/dL, and platelet count- 80x 10^9/L. Peripheral blood smear differential count- Blasts 20%, promyelocytes-4%, myelocytes-20%, metamyelocytes-12%, eosinophils-2%,basophils-3%,monocytes-4%,lymphocytes-10% and neutrophils-25% (Figure 1A). These blasts were positive for MPO. Bone marrow examination revealed presence of similar blasts as seen in peripheral blood smear having round vesicular nuclei and prominent nucleoli (Figure 1B). Flow cytometry was performed on bone marrow using CD45/SS gating strategy (Figure 2A) and 20.1% cells fell in the blast window. These blasts were positive for CD34, CD33, CD13, CD117, cytoplasmic MPO (Figure 2B-E) and negative for CD19, CD10, cytoplasmic CD79a, CD3(surface and cytoplasmic), CD4, CD8 and CD7 (Figure 2F). Additionally, CD45/SS curve showed 46.3% cells maturing towards neutrophils suggestive of immature myeloid precursors. *BCR-ABL1* translocation analysis by RT-PCR was done which was positive and showed *M-BCR-ABL1* transcript in most of the cells. Considering the clinical presentation, (massive splenomegaly) peripheral blood picture, PCR and FCM findings, a final diagnosis of CML in myeloid blast crisis was given.

Case 2

A 15-year-old male presented with dull aching pain over left hypochondrium and weakness for 10 days. Ultasonography revealed hepatomegaly and massive splenomegaly. On further evaluation patient had severe leucocytosis with WBC count of 610 x10^9/L, Hb- 8g/dL and platelet count of 970x10^9/L. Peripheral blood smear examination revealed small sized blasts constituting

Table 1: Showing Hb, Platelet count, TLC and DLC in all the three cases.

Case No.	Age/Sex	Hb	PlateletCount	WBC	DLC
1.	4 yr/F	14.2 g/dL	80 x 10^9/L	580 x 10^9/L	Blasts-20%, Promyelocytes- 4%, Myelocytes-20%, Metamyelocytes-12%, Eosinophils-2%, Basophils-3%, Monocytes-4%, Lymphocytes-10%, Polymorphs- 25%
2.	15 yr/M	8.0g/dL	970 x 10^9/L	970 x 10^9/L	Blasts-35%, Promyelocytes- 2%, Myelocytes-24%, Metamyelocytes-10%, Eosinophils-2%, Basophils-4%, Monocytes-5%, Lymphocytes-8%, Polymorphs- 10%
3.	14 yr/M	10.0g/dL	100 x 10^9/L	298 x 10^9/L	Blasts-8%, Promyelocytes- 5%, Myelocytes-25%, Metamyelocytes-15%, Eosinophils-2%, Basophils-4%, Monocytes-4%, Lymphocytes-12%, Polymorphs- 25%

Abbreviations: Hb: Hemoglobin; TLC: Total Leucocyte Count; DLC: Differential Leukocyte Count

Table 2: Showing the clinical presentation and laboratory findings of the 3 cases of pediatric CML.

Case No.	Age/Sex	CP	% Blasts		Cytochemistry		BMB	IHC	FCM (blasts+ for)	PCR (bcr-abl)
			PB	BM	MPO	PAS				
1.	4 yr/F	Splenomegaly,	20	95	+	-	Sheets of monomorphic cells, Vesicular nuclei& prominent nucleoli	Not done	CD34, CD33, CD13, CD117,cMPO	+ 210kd
2.	15 yr/M	HSM	35	85	-	+	Small sized blasts	Not done	CD10, CD19, CD34	+ 210kd
3.	14 yr/M	Massive splenomegaly, lymphadenopathy	8	40	+	-	Sheets of cells with Vesicular nuclei&prominent nucleoli	CD 34, CD 19,CD20,Anti MPO positive	Not done	+ 210kd

Abbreviations: CP: Clinical Presentation; PB: Peripheral Blood; BM: Bone Marrow; HSM: Hepatosplenomegaly; BMB: Bone Marrow Biopsy; IHC: Immunohistochemistry; FCM: Flow Cytometry

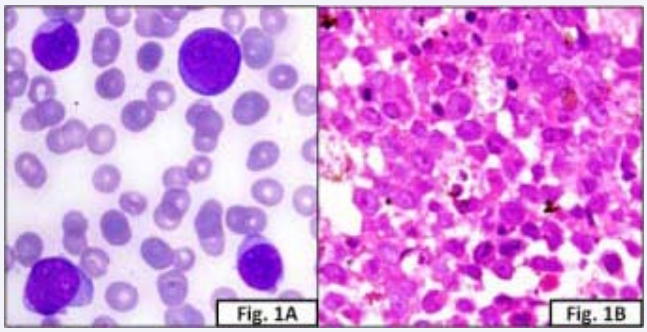

Figure 1 Figure 1A- Peripheral smear showing atypical cells/blasts with moderate amount of basophilic cytoplasm and inconspicuous nucleoli; Figure 1B: H&E section of bone marrow biopsy showing sheets of blasts

35% of total leucocytes with differential count as- Blasts- 35%, promyelocytes-2%, myelocytes-24%, metamyelocytes- 10%, eosinophils-2%, basophils-4%, monocytes-5%,lymphocytes-8% and neutrophils-10% (Figure 3A). Some of the blasts were positive for PAS stain and negative for MPO (Figure 3B,C). Subsequently bone marrow biopsy was done which showed infiltration of marrow with these blasts (Figure 3D). FCM was performed on peripheral blood using CD 45/SS gating strategy and the blasts were strongly positive for CD19 and also positive for CD10 (Figure 3E,F). They were however negative for CD34, HLA-DR, cytoplasmic MPO, CD3 (both surface and cytoplasmic), CD4, CD7 and CD8. *BCR-ABL1* by PCR was positive in 95% cells with presence of *M-BCR-ABL1* transcript. Based on the above findings a final diagnosis of CML in lymphoid blast crisis was given. The patient was started with ALL-induction therapy and on six month follow up he is doing well.

Case 3

A 14- year- old male presented with fever, headache and myalgia for one week. Patient had massive splenomegaly and lymphadenopathy on examination. Laboratory tests revealed a high TLC of 298x10^9/L, Hb- 10g/dl and platelet count of 100x10^9/L. Peripheral blood smear revealed blasts-8%, promyelocytes-5%, myelocytes-25%, metamyelocytes

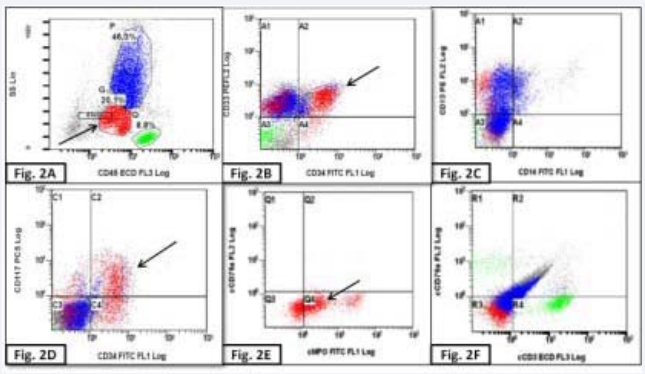

Figure 2 Figure 2A- FCM showing CD45/SS gated cells with arrow showing the blast population in red, 2B- blasts (arrows) that are positive for CD34, CD33, 2C- CD13, 2D- CD33, 2E- cMPO, 2F-cCD3 and cCD79a negative.

15%, eosinophils-2%, basophils-4%, monocytes-4%, lymphocytes-12% and neutrophils-25%. The blasts were MPO negative. A subsequent bone marrow aspirate examination revealed 40% atypical cells with high N: C ratio, moderate amount of cytoplasm, round nucleus with prominent nucleolus. No evidence of myelodysplasia was noticed in the peripheral smear or bone marrow aspirate smears. Bone marrow biopsy revealed near complete replacement of marrow with blasts showing similar morphology as in aspirate (Figure 4A). The diagnosis of CML was confirmed by PCR for *BCR-ABL1* translocation which confirmed the presence of *M-BCR-ABL1* transcript (seen on all the neutrophils and blasts). On IHC these blasts were positive for CD34 (Figure 4B), anti-MPO (Figure 4C), CD19 (Figure 4D), CD20 (Figure 4E) and negative for CD 3 (Figure 4F). Hence a diagnosis of mixed phenotypic blast crisis was made. Patient has been started on induction therapy and is on close follow up.

DISCUSSION

The incidence of chronic myeloid leukemia presenting in blast crisis in adults is approximately 10% as opposed to pediatric population where it is estimated to be less than 5% by few authors [1]. As opposed to this we found an unusually high incidence of pediatric CML presenting in blast crisis at our institution. Since the time span of this observation is short, further long term studies are needed to find out the true incidence of blast crisis in the pediatric age group.

A previous study showed that the median age of presentation of pediatric CML is 16 years with most of the patients being males

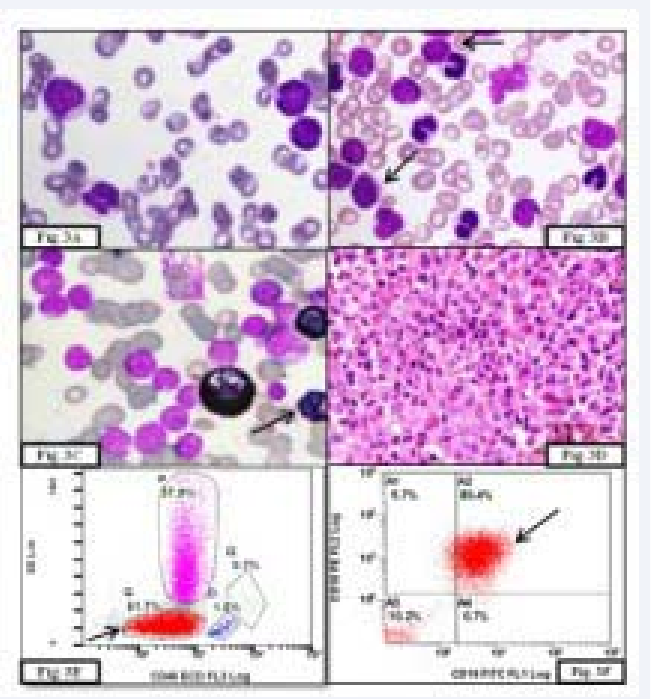

Figure 3 Figure 3A- Peripheral smear showing blasts, 3B- smear showing blasts that are PAS positive indicated by arrows with positive stain in neutrophils working as internal control, 3C- few myeloperoxidase positive blasts, 3D- bone marrow biopsy section (H&E), 3E- FCM showing CD45/SS gated cells with arrow indicating the blast population in red, 3F- blasts (arrow) which are CD10, CD19 positive.

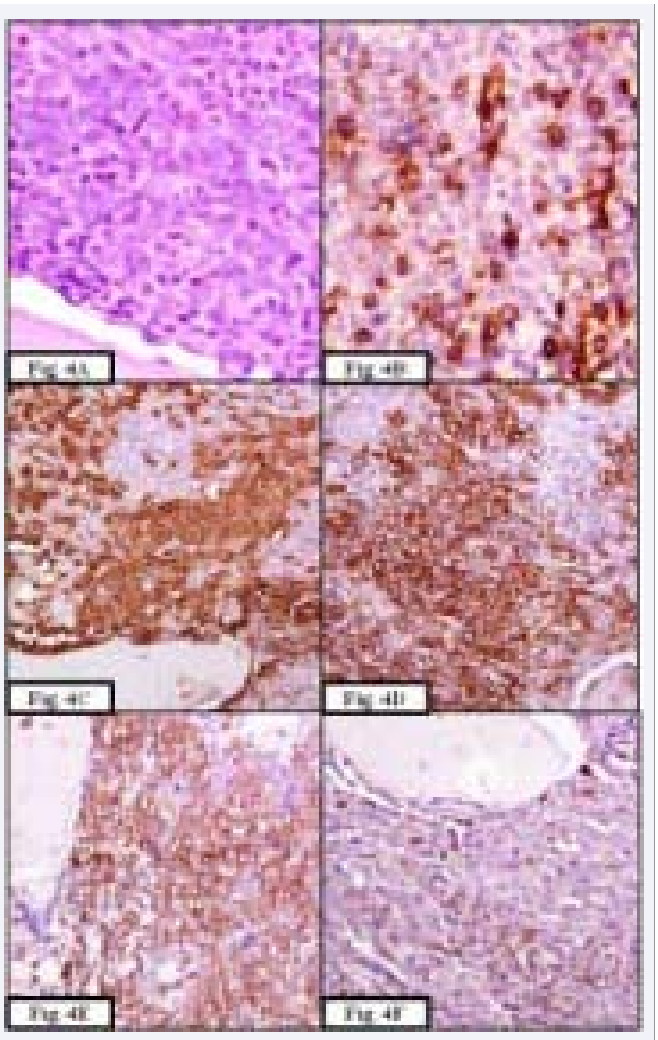

Figure 4 Figure 4A- H&E stained bone marrow biopsy section showing sheets of blasts admixed with hematopoietic cells, 4B- CD34 positivity, 4C- anti-MPO positivity, 4D- CD19, 4E- CD20, 4F- cCD3 negative.

[4]. This was in accordance with the present study. The clinical presentation and the laboratory parameters like the median hemoglobin, median WBC, and median platelet count in this age group did not differ in comparison to adults [5]. However, Frederic et al reported a higher presenting leukocyte counts in children [1].

The biology of progression of pediatric CML to BC is still not completely known, and is supposed to be similar to that of adults [3]. *BCR-ABL1* fusion transcript causes leukemic stem cells to induce granulocytic proliferation because of inherent tyrosine kinase activity as well as blast proliferation. This is partially because *c-Jun*, a monopoiesis-promoting transcription factor, is down regulated in both CML neutrophils and blasts by *BCR-ABL1* [6]. Thus, the *BCR-ABL1* fusion gene is expected to be found even in mature neutrophils in CML. In addition, mature eosinophils and basophils also carry the *BCR-ABL1*fusion gene resulting in their proliferation in CML [7].

Some acute leukemias especially ALL can also show *BCR-ABL1* translocation. The incidence of Philadelphia chromosome positive ALL is 15-30% [8]. This gain of function mutation

may also be noticed in 1-2 % of de novo AML's [8]. *BCR-ABL1* translocation is also the most common recurrent cytogenetic abnormality in mixed phenotypic acute leukemias [9]. Since the incidence of pediatric CML's presenting with blast crisis is very small, the chances of they being misdiagnosed as acute leukemia (AML/ALL) with t (9;22) is very likely. Hence, such cases (CML-BC) need to be differentiated from de novo acute leukemia's. There is no absolute parameter for the diagnosis of CML-BC vis a vis acute leukemia, however, clinical features like splenomegaly, peripheral blood leucocytosis with presence of more mature myeloid forms and absolute basophilia may suggest a CML-BC. Furthermore, the presence of *BCR-ABL1* translocation in mature neutrophils (which may be separated from blasts by ficolle-hypaque technique) will prove helpful in doubtful cases. This technique was used in one of our cases which presented as mixed phenotypic blast crisis. Further the presence of additional cytogenetic aberrations including those associated with myelodysplasia and deletions in IKZF and CDKN2A/B may aid in arriving at the right diagnosis [7]. However, cytogenetic and molecular studies could not be carried out in the above cases due to economical constraints

WHO defines MPAL on the basis of the expression of strictly specific T-lymphoid (cytoplasmic CD3) and myeloid (cytoplasmic MPO) antigens, demonstrated by flow cytometry or cytochemistry and/or clear evidence of monocytic differentiation. Since there is no single antigen strictly specific for B-cells, B-cell lineage assignment in MPAL relies on the strong expression of CD19 together with another B-cell associated marker or, in cases with weak CD19, on the expression of at least three B-lineage markers [8] In addition, the WHO recognizes two distinct categories: MPAL with the t (9; 22) (q34; q11)/*BCR-ABL1* and MPAL with t (v; 11q23)/*MLL* rearrangement. The remaining cases are designated as MPAL NOS. While MPAL with t (9; 22) (q34; q11.2) is rare, this translocation is the most common recurrent cytogenetic abnormality seen in MPAL [8]. WHO suggests caution while making the diagnosis of MPAL with t (9; 22) in a case of myeloid leukemia with maturation that also shows expression of lymphoid markers, because CML-BC may show a similar pattern, in such cases if *BCR-ABL1* fusion signals are detected by FISH/PCR in mature neutrophils as well as in blasts then CML-BC is the most likely diagnosis [9].

CML-BC should be treated with tyrosine kinase inhibitors, with or without induction chemotherapy based on the blast phenotype, with the goal of reverting the disease to chronic phase and proceeding to allogenic stem cell transplantation as soon as possible [10]. Imatinib currently is considered the best first line treatment for CML and its efficacy has been shown by various authors in the past [10]. Dasatinib is well tolerated in children and is the first drug of choice for CML-CP and CML-AP because it provides a more rapid response and greater 3 year event free survival [11].

ASCT was the standard modality of treatment but with the introduction of TKI's its use has been limited to advanced cases of CML or cases that are resistant to TKI's [11].

Newer advances are being made in the form of targeted therapy against genes involved in disease progression like JAK/STAT, JAK2kinase, protein phosphatase 2 A , arachidonate, 5-lipoxygenase gene, BCL-6 and sirtuin 1but are still in the trial phase [11].

CONCLUSION

Prognosis of blast crisis as such is very poor both in adult and pediatric CML and there is paucity of data regarding the incidence and presentation of blast crisis in pediatric CML. Since the incidence of acute leukemia in children is higher as opposed to CML-BC the chances of it being missed easily is very high. Hence, caution should be exerted while diagnosing a CML in BC as opposed to de-novo AML/ MPAL with t (9; 22) (q34;q11.2) as the treatment line for both differs and an early prompt diagnosis using ancillary aids is imperative.

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