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Childhood CML Presenting as Basophilic Blast Crisis – The First Case Series, Rare Manifestation of a Rare Disease with Review of Literature

Dr. Raghavendra H Vijay[1], Dr. Namrata N Rajkumar[1], Dr.Lakshmiah K Channagiri[2] and Dr.Vishweshwariah Lakshmidevi[1]

[1]Departments of Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

[2]Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

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Abstract

Objective: CML is a clonal stem cell disorder caused by balanced translocation between the long arm of chromosome9 and 22,t (9:22) (q34;q11) also called the Phildelphia chromosome. CML accounts for 15-20% of leukaemia in adults. Chronic leukemias are rare in childhood. Chronic myeloid leukaemia(CML) accounts for,3% of childhood leukaemia's. The natural history is bi or triphasic (BP).CML presenting as blast crisis is rare, and particularly so in children. Basophilic blast crisis is extremely rare. Purpose of the study was determined the clinical and laboratory features of childhood CML, presenting as basophilic blast crisis.

Methods: analysis was done in 2 cases of childhood CML, Bone marrow and peripheral smear was studied. Along with Cytogenetics, Molecularmethods (PCR) and Flow cytometry immunophenotyping.

Results: In both cases of childhood CML, Bone marrow and peripheral smear was suggestive of CML. Cytogenetics revealed Phildelphia chromosome in both cases with Molecular confirmation. Flow cytometry was also done in one case, confirmed the diagnosis.

Conclusion:CML constitutes approximately 3-5% of childhood leukemias. CML presenting as blast crisis is rare,and particularly so in children. Basophilic blast crisis is extremely rare. Present study is first of the kind, to report 2 cases of childhood CML presenting as basophilic blast crisis. This is yet another example of how Imatinib therapy has prolonged the survival of a child who presented in the basophilic blast crisis of CML.
Chronic Myelogenous Leukaemia(CML) in children is very rare, constitutes around 3% of leukaemia in children,and presenting as basophilic blast crisis is extremely rare. We report the first case series, of CML in a 15 year and a 10year old boys who presented as basophilic blast crisis of CML.13 cases of basophilic blast crisis of CML have been reported in adults. None in children, at presentation.The early recognition of this rare leukaemia, with availability of targeted therapy, Imatinib has improved the survival. Further studies of the breakpoint may provide insights into production and maturation of basophils.

Abbreviations: CML:Chronic Myeloid Leukemia; PCR:Polymerase Chain Reaction; Ph+: Phildelphia Chromosome; PS:Peripheral Smear.

Keywords: Chronic MyelogenousLeukemia CML, Child,Basophilic Blast Crisis, At Presentation.

Introduction

CML are extremely rare in childhood, constitutes around 3% of leukaemias in children. We studied clinical and laboratory features of 2 cases of CML in children, presenting as basophilic blast crisis, including PS, Bone marrow aspiration, Cytogenetics, PCR and flow cytometry were studied in detail.

Chronic Myelogenous Leukaemia(CML) is a myeloproliferative neoplasm consistently associated with the BCR-ABL 1 fusion gene located in the phildelphia (Ph) chromosome [1].The natural history is bi or triphasic (BP).Blastic phase is characterized by greaterthan 20% blasts in the peripheralblood (PB)bone marrow, (BM) or extramedullary site [1].The blast lineage is myeloid in 70% of cases .However basophilic blast crisis is extremely rare. We describe 2 cases first case was a 15yr old child,2nd case was 10year old boy with aninitial presentation as basophilic blast crisis in CML. As far we can ascertain, this is first reported series of childhood CML with a rare presentation. We discuss these cases with available world literature.

Case:1

A 15 year old boy was referred to our institute, a tertiary cancer centre in South India with history of fatigue and abdominal mass in 2013.On examination salient clinical findings of pallor, icterus and massive splenomegaly, no symptoms attributable to increase histamine such asurticaria, peptic ulcer or asthma were reported. Hemogramrevealed haemoglobin7.4g/dl, total count, 2.34,300/cumm, with differential count of blast 30%,basophil 60%, platelet count 1,14,000/cumm. LFT was with in normal range except for total bilirubin 3mg/dl.Serumelectrolytes, renal function tests, blood glucose levels, LDH, Uric acid were with in normal limits. Chest X-ray was normal. Toludine blue showed metachromatic granules characteristic of basophil. BM examination was done which showed a higher blast count 65% (Figure 1).Cytogenetic analysis revealed a karyotype of 47XY,t(9;22)(q34:q11.2),+der(9)t(9;22)(q34;11.2),i(17)(q10)(06)/46,XY,t(9;22)(q34;q11.2)(04). BM was subjected to flow cytometry, the blasts expressed myeloid markers CD 13,CD33,CD117,CD38,and CD123inaddition to CD34 and were negative for Tdt, CD5, CD3, CD7, CD19, CD10, CD79b, CD25 and MPO (Figure 2). PCR analysis showed BCR/ABLP210 and transcript. With these findings diagnosis of basophilic blast crisis was made and was started on chemotherapy and Imatinib 400mg/day. After 18 months of follow up patient is well and in clinical, hematological and molecular remission.

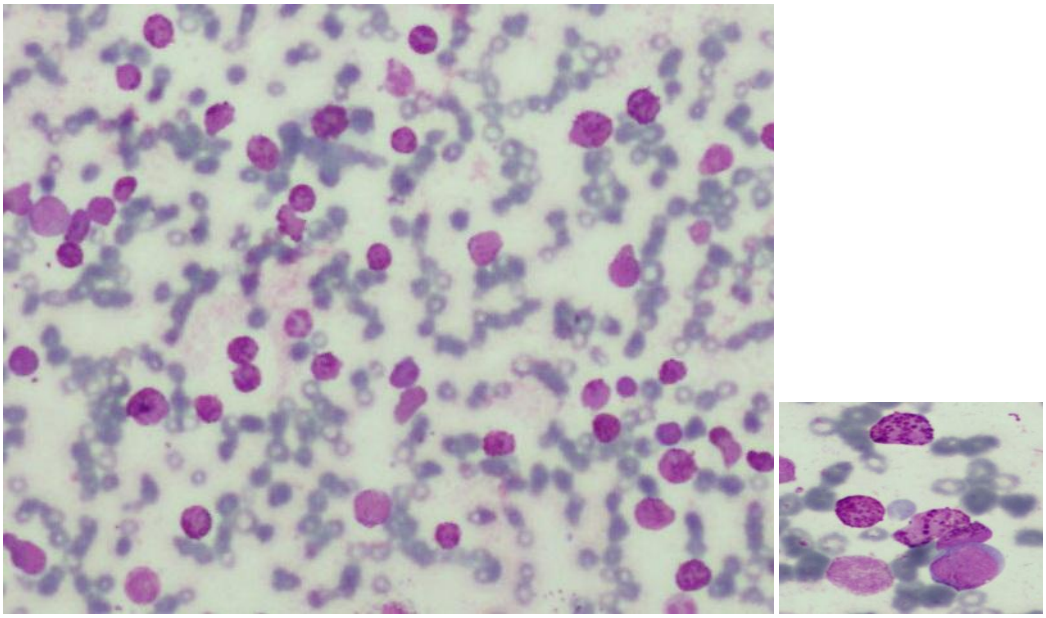

Figure 1: Bone marrow aspiration showing blasts and basophils.

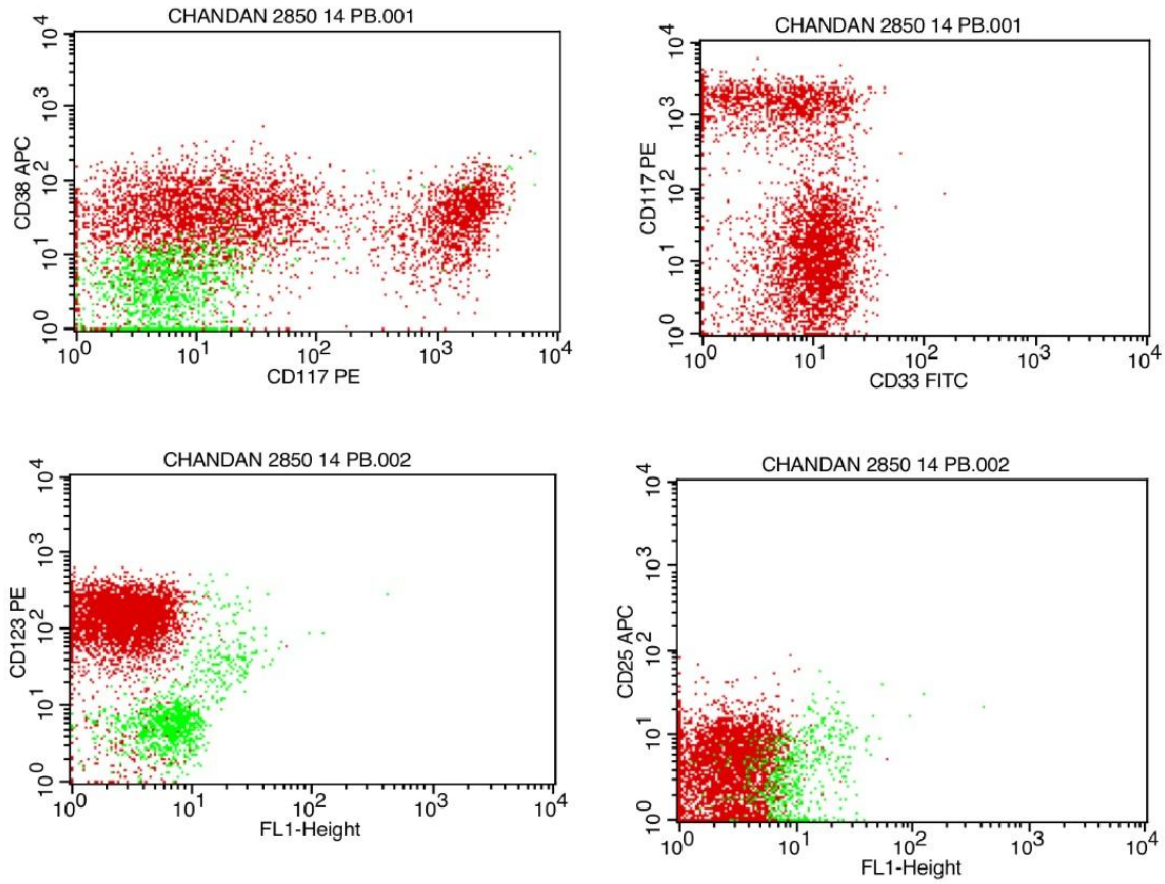

Figure 2: Blast Positive for CD 38, CD 117, CD 33 and CD 123.

Case: 2

A 10 year old boy was referred to our institute, he was a known asthamatic on treatment, he presented with history of fatigue, itching of the body with abdominal mass. On examination salient clinical findings of pallor, icterus and massive splenomegaly was noted. Symptoms attributable to increase histamine such as urticaria, and asthma were reported. Hemogram, revealed haemoglobin 8.4g/dl,total count 1,30,300/cumm, with differential count of blast 40%,basophil 50%, platelet count 94,000 /cumm . LFT was with in normal range except for total bilirubin 5mg/dl. Serum electrolytes, renal function tests, blood glucose levels, LDH,Uric acid were with in normal limits. Chest X-ray was normal. BM examination was done which showed a higher blast count 60%.Cytogenetic analysis revealed a karyotype of47XY,t(9;22)(q34:q11.2). However no additional cytogenetic abnormalities were noted. The bone marrow sent for qualitative RT-PCR, revealed the hybrid transcript for BCR-ABL, Genomic Breakpoint observed e14a2 corresponding to p210.With these findings diagnosis of basophilic blast crisis was made and was started on chemotherapy and Imatinib 400mg/day. After a few days of follow-up, patient succumbed to the disease.

Discussion

CML in blastic phase is the transition of CML in chronic or accelerated phase to an acute leukaemia, characterized by >30% blasts in the bone marrow or peripheral blood or extramedullary disease outside of the spleen [2].Blast percentage was brought down to 20% by the WHO working group in2008. In approximately 70% of cases, the blast lineage is myeloid and may include neutrophilic, basophilic, eosinophilic, monocytic, megakaryocytic or erythroidblasts or any combination thereof, whereas approximately 20-30% of cases blasts are lymphoid [1].Basophilic blast crisis is extremely rare,and particularly so in children. Reports in the literature of such cases are very few all the cases which have been reported are in adults and they all have progressed from CML in chronic phase. Our cases are unique, as these cases are in children, case 1 was a 15year,and 2nd case was a 10year old boy, whose initial presentation was in basophilic blast crisis. 13 case reports of basophilic blast crisis of CML have been reported in adults. The clinical features, laboratory findings and karyotypic abnormalities have been detailed in table [3].

age	sex	Total count	BM(Baso%)	AP to Death in months	add.ch.abnormal	progression
59	F	70000	NR	3	NR	+
39	M	27200	27.8	2.5	+	+
65	M	60200	NR	5	+	+
31	M	34000	57	3	+	+
47	M	16100	19.6	1.3	+	+
46	M	13600	37	3	NR	+
27	M	17700	NR	2.5	+	+
55	M	24300	-	4.2	2	NR
77	F	93000	-	33.2	5	+
50	F	47880	-	29	1.5	+
43	M	20500	-	NR	6	NR
37	F	57800	-	20.6	5.5	+
29[5]	M	1,09,000	-		NR	
15	M	2,34,000	65%	Remission at 18months followup.	47XY,t(9;22)(q34:q11.2),+der(9)t(9;22)(q34;11.2),i(17)(q10)(06)/46,XY,t(9;22)(q34;q11.2)	+At presentation
10	M	1,30,000	60%	Died in 2 weeks	NR	+At presentation

Table: 3

Some authors have indicated hyperhistemenemia is associated with poor prognosis [3,4].We can speculate that the presence of splenomegaly and absence of hyper histaminic symptoms in the first case have been associated with the relative longer survival [5].Of course the Imatinib therapy would be the paramount reason for good prognosis. Slovak ML, et al. have described 69 cases of AML/MDS with t (6;9) [6].Pearson etal. have described 9 cases with basophilia associated with t(6;9), it's interesting to know breakpoint in 9q involves same chromosomal band as that in t(9;22) seen in CML, in which increased basophils are well known [7].Further studies of the breakpoint may provide insights into production and maturation of basophils. There is balanced reciprocal translocation between the long arms of one of the chromosomes9 and 22.Between the regions q34 and q11.2 respectively, suggestive of phildelphia positive chromosome complement, Additional chromosomal abnormalities were seen in 10 cases, with a double Ph being the commonest. The bone marrow sent for qualitative RT-PCR, revealed the hybrid transcript for BCR-ABL,Genomic Breakpoint observed wase14a2 corresponding to p210,along with an extra derivative 9 and isochromosome of long arm chromosome of 17 at the region q10 found in 60% of the metaphases studied. Remaining 40% cells also show balanced reciprocal translocation between 9 and 22.He was treated with combination chemotherapy with 3 cycles of daunorubicin 60 mg and 7 cycles of Cytosine arabinocide (cytosol) 200mg once daily followed by 4 cycles of high dose Arac C 4gm once daily with Imatinib400 mg once daily. All but one of the cases [5] were in the preImatinib era and survived for only few months(1.3-5.5 months),Our first patient is alive and well 18 months after the diagnosis. This is yet another example of how Imatinib therapy has prolonged the survival of a child who presented in the basophilic blast crisis of CML.

To our knowledge 10 studies have reported clinical and biological data in patients who were younger than 20 years and had CML. There are very small numbers of children in children in most of these reports published between 1962 to 2005 [1].

CML are extremely rare in childhood, constitutes around 3% of leukaemia in children. Its rarity was established by the following facts. A phase one study from the children's oncology group included 31 patients from 23 centres, signifying the rarity of CML in this age group. A comparison between Imatinib and stem cell transplant (SCT), as a therapy for childhood CML, included 30 patients in the IMA arm and 18 patients in the SCT arm [8]. In other studies, the patient number varied from 4 to 39 [8].None of these studies had basophilic blast crisis at presentation.

Conclusion

CML constitutes approximately 3-5% of childhood leukaemia. CML presenting as blast crisis is rare, and particularly so in children, Basophilic blast crisis is extremely rare. Present study is first of the kind to report 2 cases of childhood CML presenting as basophilic blast crisis.

This is yet another example of how Imatinib therapy has prolonged the survival of a child who presented in the basophilic blast crisis of CML.

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