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Research Article

Barely encountered

Basophilic Blast crisis of CML- Barely encountered

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Objective: Chronic leukemias are rare and blastic phases of CML are even rare. Immunophenotyping/IHC studies have a limited role in the diagnosis of CML but are being used in CMl blast transformations. The purpose of this current study was to report the barely encountered basophilic blast crisis of CML and to determine the clinical and laboratory and Flow immunophenotyping (FIC)/IHC features of the blast crisis.

Methods: 8-year retrospective study, Patients were evaluated at KMIO between 2004 to 2012. Total out of 688 clinically suspected as CML,488 cases were diagnosed as CML, and 42 cases of peripheral smear suspected of blastic phase CML were chosen for the study. Bone marrow, Karyotyping and Molecular confirmation were available with IHC /FIC in 15 cases.

Results: adults and Male sex predilection was seen. The gender ratio was 1.6:1. The splenomegaly& leukocyte count> 200X10° I was seen, and in all cases, bone marrow aspiration confirmed the diagnosis, and most cases of CML progressed to the blastic phase from the chronic phase during their course of treatment. Philadelphia chromosome was noted in most cases and 6 cases revealed additional markers.PCR revealed a p210 transcript in all cases. In 15 cases in the blastic phase Flow cytometry immunophenotype/IHC was done. 9 cases were myeloid blastic phase,2 cases were reported as basophilic blast crisis single case was mixed phenotype, 3 cases were lymphoid blastic phase.

Conclusion: blast crises of CML are rare, more so are Basophilic blast crises of CML, ancillary tests to bonemarrow studies like IHC/FIC /PCR aid in the quicker diagnosis, in the blastic phase and aid in deciding the treatment. Further studies of the breakpoint may provide insights into the production and maturation of basophils.

Keywords: Chronic myeloid leukemia, Polymerase chain reaction, Flow cytometry

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Introduction

Chronic myelogenous leukaemia (CML) is myeloproliferative neoplasm consistently associated with BCR-ABL 1 fusion gene located in Philadelphia (Ph) chromosome [1]. The natural history is bi or triphasic(BP). The blastic phase is characterized by greater than 20% blasts in peripheral blood(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 case of child,15yr old, with an initial presentation as basophilic blast crisis in CML. The other case was an adult 40year, known case of CML on follow-up, discontinued treatment due to financial constraints .and we discussed blastic phase of CML, along with these 2 rare basophilic blast crisis cases in detail laboratory features including clinical features, PS, BMA, FCI/IHC with note on BCR-ABLtranscripts review with available world literature.

Methods

We reviewed records of CML Between 2004 to 2012 received by Department of Pathology. Peripheral smear/BMA collected in suspected CML in blastic phase in 42 cases age ranged from youngest 9 years to oldest 67 years. , BMA /bone marrow biopsy of this blastic phase of CML was included in study. All non-blastic phases of CML were excluded. Bone marrow, Karyotyping and Molecular confirmation were available and IHC /FIC was also available in 15 cases. Bone marrow aspiration, cytogenetics, PCR and flow cytometry confirmed diagnosis. Clinical features were recorded. Anaemia was diagnosed when hemoglobin was < 10g dL. Leucocyte count >200X10^9/L.Thrombocytopenia< 150x10^9 . was seen in most cases, Reports of.IHC /FIC/BCR -ABL transcripts were reviewed.

Results

Abdominal fullness and pain were most common symptoms marked as splenomegaly, Adults and male preponderance were seen. Splenomegaly was predominant finding occurring in 95% of patients. The median size measured on ultrasound was 17 cm. Mild to moderate hepatomegaly on USG was seen in most patients. Blood tests for HIV, HBsAg and HCV were negative. Serum LDH levels range normal 35U/L to as high as 77800/L.Serum Alkaline phosphatase was within normal range in all cases. Hemoglobin value ranged from (5.5-10.g/dL). Anaemia, WBC count raised, thrombocytopenia.was frequently seen. CML was Classified according to WHO criteria, Bone marrow analysis revealed a blastic phase (fig1) Bone marrow basophilia 6% was seen in all blast crisis cases.

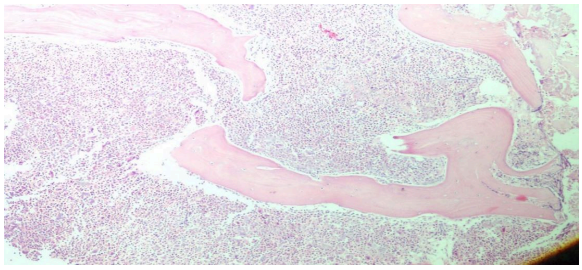

Figure 1: 20x H&E Showing increased blasts in bone marrow

Blast varied from 20% to 70% in most cases, myeloid BP showed myeloid markers positivity and lymphoid BP revealed lymphoid markers positivity. 2 cases had basophilic blast crisis, basophil 40 to 60% along with blast of 30%. First case of basophilic blast crisis was 15-year-old boy who was referred to our institute,

Tertiary cancer centre in South India with history of fatigue and abdominal mass. On examination of salient clinical findings of pallor, icterus and massive splenomegaly, no symptoms attributable to increased histamine such as urticaria, peptic ulcer or asthma were reported. Hemogram hemoglobin 7.4g/dl, total count,2.34,300/cumm, with differential count of >blast 30 %, basophil 60%, platelet count 1,14,000 /cumm. LFT was within normal range except for total bilirubin 3mg/dl. Serum electrolytes, renal function tests, blood glucose levels, LDH, and Uric acid were within normal limits. Chest X-ray was normal. Toludine blue showed metachromatic granules characteristic of basophil. BM examination was done which showed higher blast count of 65 %.Cytogenetic analysis revealed 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, Followed by IHC on bone marrow biopsy blasts expressed CD 34, myeloid markers, CD117, CD38, and MPO (fig 2) and were negative for Tdt, CD5, CD3, CD7, CD10, CD79b, CD20 (fig3)

Figure 2: 20x MPO positive blasts

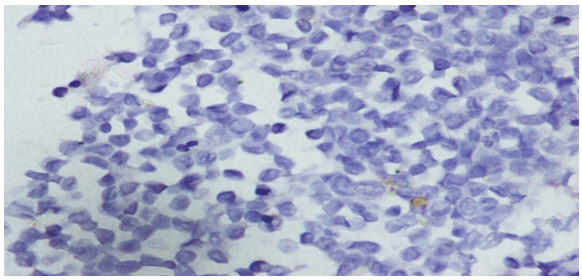

Figure 3: CD20 being negative.

PCR analysis showed BCR/ABL P210 and transcript, diagnosis of basophilic blast crisis was made and was started on chemotherapy and Imatinib 400mg/day. After > year of follow up patient is well and in clinical, hematological and molecular remission. Another case was 40-year-old man who presented with fatigue and a mass abdomen. On examination of salient clinical findings of pallor, and massive splenomegaly, no symptoms attributable to increased histamine such as urticarial, peptic ulcer or asthma were reported. Hemogram hemoglobin 9.4g/dl, total count,3.39,300/cumm, with differential count of blast 40 %, basophil 40%, platelet count 1,14,000 /cumm. LFT was within normal range. Serum electrolytes, renal function tests, blood glucose levels, LDH, and Uric acid were within normal limits. Chest X-ray was normal. Toludine blue showed metachromatic granules characteristic of basophil. BM examination was done which showed blast count of 40 % (, fig 4)karyotyping was not done, and patient was lost for follow-up.

Discussion

Most cases of CML terminate in blast crisis typically as myeloid blast crisis.1/3rd are lymphoblastic, less commonly seen are erythroblasts, monocytic, and barely encountered are basophilic blast crises.[3&4]

CML in blastic phase is transition of CML in chronic or accelerated phase to acute leukaemia, characterized by >30% blasts in bone marrow or peripheral blood or extramedullary disease outside of spleen. Blast percentage later was brought down to 20% by the WHO working[1]. In approximately 70% of cases, the blast lineage is myeloid and may include neutrophilic, basophilic, eosinophilic, monocytic, megakaryocytic or erythroid blasts or any combination thereof, whereas approximately 20-30% of cases blasts are lymphoid1. Basophilic blast crisis is extremely rare, Reports in the literature of such cases are very few cases, which have been reported in adults and they all have progressed from CML in the chronic phase, Our first case is unique, in that this was a 15year child, whose initial presentation was in basophilic blast crisis. A dozen cases of basophilic blast crisis of CML have been reported in adults. The clinical features, laboratory findings and karyotypic abnormalities have been detailed.

Some authors have indicated hyper histemenemia is associated with poor prognosis[3&4]. We can speculate that the presence of splenomegaly and the absence of hyperhistaminic symptoms may have been associated with the relatively long survival of our first patient. Cml progresses to Myelo fibrosis [5] Of course Imatinib therapy would be the paramount reason for a good prognosis. Slovak M L et al have described 69 cases of AML/MDS with t(6;9)[6]. Pearson et al have described cases with basophilia associated with t(6;9)[7], It was interesting to know breakpoint in 9q involves the same chromosomal band as that in t(9;22) seen in CML, in which increased basophils are well known. Further studies of the breakpoint may provide insights into the production and maturation of basophils. There is a balanced reciprocal translocation between the long arms of one of the chromosomes 9 and 22. between the regions q34 and q11.2 respectively, suggestive of phildelphia positive chromosome complement, Additional chromosomal abnormalities were also seen, with a double Ph being the commonest. The bone marrow sent for qualitative RT-PCR revealed the hybrid transcript for BCR-ABL was detected. Genomic Breakpoint observed e14a2 corresponding to p210, along with an extra derivative 9 and isochromosome of long arm chromosome of 17 at the region q10 found in 70% of the metaphases studied. Remaining 30% of cells also show balanced reciprocal translocation between 9 and 22. He was treated with combination chemotherapy with Imatinib400 mg once daily. Blastic phase of CML, prognosis is poor[8,9,10]. Most patients in the blastic phase are alive> 8 months of follow up and Our basophilic blast crisis is alive and well 12 months after the diagnosis. This is yet another example of how Imatinib therapy has prolonged the survival of, those who presented in the basophilic blast crisis of CMLand ancillary tests will aid in the treatment decision..

Conclusion

Invariable CML progresses to the Blastic phase during follow-up, indicating a less favourable prognosis.BP common Myeloid blastic phase, Basophilic blast crisis is extremely rare, and ancillary tests/bonemarrow studies like IHC/FIC /PCR aid in the quicker diagnosis, in the blastic phase and also aid in deciding the treatment. Further studies of the breakpoint may provide insights into the production and maturation of basophils.

Abbreviations: CML; chronic myeloid leukemia, BP;Blastic phase, BMA;Bone marrow Aspiration, IHC ; Immunohistochemistry, PCR; Polymerase chain reaction

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