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PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOGENOUS LEUKEMIA IN CHILDHOOD:A RARE CASE REPORT

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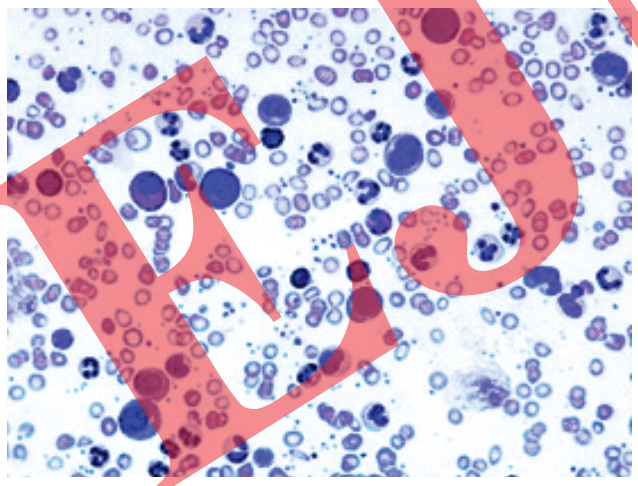
ABSTRACT
CML is a clonal hematopoietic stem cell disorder. As per WHO classification, CML is included in Myeloproliferative disorder. Adult type - CML is rare in childhood constituting about 3% of childhood leukaemia. We have reported such a case in a 7yr old male child. Peripheral blood smear and bone marrow revealed features of chronic myeloproliferative disorder and cytogenetic analysis has proved Ph chromosome positivity. We report one such case of Philadelphia positive CML in a 7 year old male patient with chief complaints of fever on & off since 4-5 months and sense of abdominal fullness since 1 month, on examination pallor was found with mild hepatomegaly and moderate splenomegaly. The clinical differential diagnosis was malaria, storage disorder or tropical splenomegaly. Though biological behaviour and prognosis are identical to that of adult type, we are reporting this case because of its extremely uncommon incidence.

KEYWORD: Chronic Myelogenous Leukaemia, Philadelphia positive CML, Clonal, Hematopoietic stem cell disorder

INTRODUCTION
Pediatric CML is the condition of chronic myeloid leukemiaoccuring in infants and children. The median age at diagnosis of chronic myelogenous leukemia (CML) is 60 to 65 years in Western registries,1 and CML in childhood is extremely rare.The disease seldom occurs in infants less than 6 months of age. CML constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these 2 age groups, respectively.2 As a child ages, the incidence of CML increases with children one to fourteen experiencing the disease at a rate of 0.7 cases out of a million children, and teenagers experiencing the disease at a rate of 1.2 cases per million. The term "children" is associated with a number of definitions, we refer to the pediatric patient as one between the ages of 0-14 years, and adolescent patients as those 15-19 years of age. There appears to be no ethnic or genetic predisposition. Although ionizing radiation is a risk factor for development of the disease, this and other environmental exposures have not been demonstrated to be causal in children.[3] While the community is grateful that CML in children and teenagers is considered ultra rare, its scarcity creates difficulty for scientists and hematologists who study and treat the disease, as well as families who need community support. Children are known to present with a higher median WBC count, although otherwise present nearly identically to adults.4,5 CML most commonly presents with fatigue, asthenia, and splenomegaly.4-6 Symptoms and signs of bone marrow infiltration or hyperleukocytosis may also be seen in more advanced cases. The natural history of pediatric CML progresses through 3 phases, similar to adult CML. Chronic phase (CML-CP) results in expansion of hematopoiesis and is defined by less than 10% bone marrow blasts. Children with CML-CP typically present with leukocytosis, anemia, and thrombocytosis.4 Children tend to present with higher WBC counts than adults, with a median WBC count of 250 000 × 10^3/μL.4,5 According to the WHO classification, accelerated phase (CML-AP) is defined by the following: 10% to 19% bone marrow blasts, peripheral blood basophils more than 20%, persistent thrombocytopenia (< 100 × 10^9/L or thrombocytosis (> 1000 × 10^9/L), increasing spleen size or increasing WBC count unresponsive to therapy, or cytogenetic clonal evolution.7 CML-AP occurs less commonly in pediatrics. Blast crisis (CML-BC) presents as overt acute leukemia and is defined by more than or equal to 20% bone marrow blasts or extramedullary blast proliferation.7

CASE REPORT

It is a case of 7 yrs old boy presented to pediatric OPD with chief complain of fever on & off since 4-5 months and sense of abdominal fullness since 1 month, on examination pallor was found with mildhepatomegaly and moderate splenomegaly. The patient was well immunized as per schedule.On examination, the patient was averagely built and averagely nourished. Local examination revealed hard and distended abdomen. Liver was palpable 7 cms and huge splenomegaly was noted of 18 cms. The patient was admitted in pediatric ward with differential diagnosis of malaria, kala azar, haemolytic anemia or tropical splenomegaly.Routine hemogram was carried out, whichrevealed Hb 5.1 gm/dl. On peripheral smear, blood picture shows markedly increased total leukocyte count (2,38,000/cmms) with all range of immature cells of myeloid lineage in differential including myeloblasts (04 %) myelocytes (11%) and metamyelocytes (07%). Mature polymorphs 71 %, lymphocytes 02% and monocytes 02%, eosinophils (01%)are seen. Basophilia (02%) is also seen. Platelet count was 2,88,000/cmms. An impression of Chonic Myeloproliferative Disorder(Chronic Myeloid Leukemia -Chronic Phase) is given with an advice of bone marrow and karyotyping.



On bone marrow examination, smears were hypercellular with absolute increase in numbers of myeloid precursor cells. Erythropoiesis was normoblastic. M:E ratio was quite high 32:1. Megakaryocytes were plentiful and show active platelet formation. Few mature lymphocytes and occassional plasma cells are seen suggestive of Chronic Myeloid Leukaemia.

Then karyotyping is done and chromosomal analysis showed46,XY,t(9q;22q) on a total of 10 metaphases, and all metaphases were found to be Ph-Positive(100%).This further confirmed our diagnosis of Ph positive CML in this case.

The hybrid transcript for BCR/ABLwas quantitated using Minor Groove Binder Real Time RT-PCR assay. It showed that specimen had 67.45% (high) Major BC R-ABL fusion transcript(210).

DISCUSSION

Amongst childhood leukemias, chronicmyeloid leukemia (CML), is a rare entity withan annual incidence of one case per millionchildren[5].CML like picture in childhood can be found in one of the two clinically distinct syndromes i.e.adult type CML (ACML) andjuvenile CML, also known as Juvenile Myelomonocytic Leukemia (JMML).

CML occurring in children is called as adult form CML, which has the same clinical, morphologic and cytogenetic findings as adult Ph positive CML occuring in adult population. Three phases have been described for CML. Most patients are diagnosed in the first phase,called the chronic phase with median duration of 4-5 years. It can develop over time into the second- accelerated phase (6-8 months) and third-blast crisis phase (3-9 months)[8]. Accelerated and blast phase has worstprognosis. This needs to be differentiated from the other form of myelodysplastic/myeloproliferative disorder like Juvenile Myelomonocytic Leukemia (JMML) because this disease mimics morphologically and clinically most closely to CML, but with a strong exception regarding the age of affection. According to WHO classification, JMML is one of the bridging MDS/MPD category of myeloid neoplasms[7]. JMML represents 18-36% of MDS in children and about 2% of hematologic malignant neoplasms. It occurs predominantly in infants and young children less than 2 years[9]. In JMML ,clinically patients presents with constitutional symptoms hepato-splenomegaly, and a maculopapular skin rash in 50%. Morphologically, there is a myelo-monocytic proliferation in the blood and bone marrow, with accompanying thrombocytopenia and anemia. Eosinophilia and basophilia are observed in minority of the patients[7,9]. Additional lab studies may show elevated haemoglobin F for age , and polyclonal hyper-gammaglobulinemia. According to the 2016 revision of WHO classification of myeloid neoplasms and acute leukemia, three criteria among four mandadotry diagnostic criteria of JMML are similar to that CML-Chronic Phase, except the one demonstration of absence of the BCR –ABL fusion protein. Thus as in this case, BCR –ABL fusion is found on karyotyping, so we classified it as typical adult type CML in childhood.

As in this case the clinical picture could not clearly diagnose the condition but as soon as morphological

findings and moreover cytogenetic study reports arrived the picture became very clear and the diagnosis made was Adult type of CML.The hybrid transcript for BCR/ABL quantification assay further confirmed the diagnosis of ACML as the Major BCR-ABL fusion transcript shows 210 kDa protein which is found in virtually all childhood CML cases. Sinniah D et al[10] have reported only 5 casesof ACML out of 168 cases of leukemia in 13 year review. So indeed its a very rare entity.

Our patient was given imatinib one of the most popular tyrosine kinase inhibitor and was well tolerated by the child until this case report is being submitted, whereas in other studies like Sinniah D et al, cases have been treated with busulphan and intrathecal methotrexate. Median survival in all cases has been 30 months due to acute leukemiatransformation and septicemia. They have stated that outlook for ACML remains poor and treatment needs re-evaluation[10].Mishra A et alreported similar findingsfor Ph positive CML in a child[11].

Allogenic bone marrow transplant is the most successful therapy if a suitable HLA identical donor is available for chronic phase CML [12]. For patients without a suitable donor, control of the disease with chemotherapy is the best current alternative [7,8, 12]. The same progress in the recent therapeutic strategy for older adults with haematological malignancies has also seen in younger adult

CONCLUSION

We have diagnosed the adult CML on routine peripheral smear examination and supported by bone marrow and cytogenetic study. Though biological behaviour and prognosis are identical to that of adult type, we are reporting this case because of its extremely uncommon incidence in childhood

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