

Atypical chronic myeloid leukaemia in an adolescent Nigerian: a case report and review of the literature

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Abstract

Atypical chronic myeloid leukaemia (aCML) is a rare subtype of CML which is now regarded as a separate clinical entity and classified among the Myeloproliferative/myelodysplastic syndromes. It lacks the Philadelphia chromosome and BCR-ABL fusion gene found in the classical CML. We report a case of aCML which was diagnosed and managed at the Haematology Department of the University of Ilorin Teaching Hospital, Ilorin. Full blood count showed anaemia, leucocytosis and presence of various forms of myeloid cells with dysplastic features. Bone marrow aspiration done also showed myeloid hyperplasia with dysplastic changes in the myeloid cells. There was poor outcome in the patient. This case illustrates the importance of full haematological investigations of suspected CML cases so that the diagnosis of a CML will not be missed or passed for CML as this could influence choice of treatment and prognosis of patients. There is need for improved diagnostic facilities in tertiary health institutions in the country if we must achieve proper diagnosis and characterization of cases of aCML.

Keywords: Atypical, CML, Adolescent, Nigerian, Review

Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder characterized by overproduction and accumulation of immature, intermediate and mature myeloid cells in peripheral blood and bone marrow^{1,2}. The hallmark for its diagnosis is the presence of the Philadelphia chromosome, t(9;22)(q34;p11), which is formed from a reciprocal translocation with juxtaposition of genetic materials between the long arms of chromosomes 9 and 22. The Abelson (Abl) oncogene on chromosome 9 becomes translocated to the Break point cluster (Bcr) region on chromosome 22 to form the Bcr/Abl chimeric gene. The BCR-ABL gene encodes a protein with

deregulated tyrosine kinase activity which then causes uncontrolled production of myeloid cells in the bone marrow and their accumulation in the peripheral blood^{2,3}.

Atypical chronic myeloid leukaemia (aCML) is a rare subtype of CML which is now classified among the Myeloproliferative /myelodysplastic syndromes according to the 2008 World Health Organization (WHO) classification of haematopoietic malignancies^{4,5}. It is regarded as an overlap syndrome showing both the myelodysplastic and myeloproliferative features in the peripheral blood and bone marrow, and lacks the Philadelphia chromosome as well as the BCR-ABL fusion gene found in the regular CML⁶.

Atypical CML is majorly a disease of the elderly with a median age of 65 years, but some cases have been reported in young adults and even in children⁷. The 2008 WHO classification defined the diagnostic

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criteria for aCML as: persistent leucocytosis $\geq 13 \times 10^9/L$ with immature circulating myeloid precursors ($\geq 10\%$ of leucocytes) with marked dysgranulopoiesis, and absent or minimal monocytosis, basophilia or eosinophilia. Dysplastic myeloid maturation is a prominent feature in aCML and differentiates it from the other myeloproliferative/myelodysplastic syndromes such as chronic myelomonocytic leukaemia (CMML) and chronic neutrophilic leukaemia (CNL) ^{5,6}.

In contrast to the usual CML, the Philadelphia chromosome and BCR-ABL fusion gene are absent in aCML, though some other non specific cytogenetic abnormalities including trisomy 8, trisomy 13, mutations in the CSF3R and SETBP 1 genes among others have been reported ^{8,9,10}. The actual incidence of aCML is unknown, however, the estimated incidence in the adults and elderly is said to be low, with only 1-2 cases diagnosed for every 100 cases of CML ¹¹. Unlike CML, aCML has been reported to progress more rapidly to acute leukaemias in up to 40% of cases with median survival time below 20 months which contrasts sharply with the median survival time of 5-10 years for the BCR-ABL positive CML ^{7,11}.

Due to the absence of the Philadelphia chromosome in aCML, the conventional tyrosine kinase inhibitors are of little value in the treatment of the disease, and poor response has also been reported for the other forms of cytoreductive treatment like hydroxyurea thereby suggesting a separate pathogenic mechanism from CML ¹². Two studies had reported the use of Decitabine and Ruxolitinib, which are hypomethylating agents, followed by haemopoietic stem cell transplantation in the treatment of their patients with variable results ^{13,14}.

There had been several studies and case reports of aCML from other parts of the world ^{7,8,9,10,11,14,15}. From literature search, there was no single case of aCML reported from Nigeria. The aim of this study, therefore, was to present a case report of a patient who was diagnosed and managed as aCML at the Haematology Department of the University of Ilorin Teaching Hospital, Ilorin. This is intended to increase awareness and encourage haematologists across the country to exercise a high index of suspicion and closely look into the diagnosis of CML such that cases of aCML will not be passed for CML.

Case Report

The patient, F.D. was a 21 year old Yoruba female student of the Kwara State Polytechnic, Ilorin, Nigeria. She presented at the Haematology Clinic of the Department of Haematology, University of Ilorin Teaching Hospital (U.I.T.H.), Ilorin on 2nd March 2012 with 2 days history of headaches and abdominal pain. The patient was first seen in a private hospital in town 2 weeks prior to presentation where she complained of fever and abdominal pains and a full blood count (FBC) done showed increased white blood cell (WBC) count. She was prescribed some antibiotics and antimalarial drugs and then referred to the haematologist on account of the observed leucocytosis. At presentation in the Haematology clinic, patient still complained of slight fever, body weakness, headaches and abdominal pain. Full history taking and physical examination was carried out. The abdominal pain was said to be sharp and colicky in nature and associated with a progressive swelling of the abdomen. Abdominal pain was localized to the left side of the abdomen, aggravated by walking or prolonged standing but is relieved by lying supine or analgesic use. The pain did not radiate to the back and was not associated with diarrhea, constipation or vomiting. Headaches was said to be dull, felt more in the fore head and was not associated with dizziness, blurring of vision or photophobia. There was history of slight fever at onset of illness which responded to analgesic ingestion. There was no history of jaundice, bleeding or passage of dark coloured urine.

Physical examination revealed a young lady, slightly febrile to touch (body temperature was 36.8°C), pale, anicteric, acyanosed and there were no subconjunctival or petechial haemorrhages seen. There was palpable splenic enlargement of 10cm below the left costal margin, but no significantly palpable hepatomegaly or lymphadenopathy. Patient was admitted to the ward for investigations and management.

A full blood count was done which showed packed cell volume (PCV) 21%, total white blood cell count $29.1 \times 10^9/L$ with the following differentials – Myeloblast 8%, Promyelocytes 10%, Myelocytes 20%, Metamyelocytes 20%, Neutrophils 25%, Lymphocytes 5%, Eosinophils 10%, Basophils 1% and Monocytes 1%. Peripheral blood film examination showed leucocytosis with presence of blasts, promyelocytes,

myelocytes, metamyelocytes, neutrophils, basophils, monocytes and lymphocytes. Dysplastic changes were observed in the immature myeloid cells. A bone marrow aspiration study was also done which showed myeloid hyperplasia with dysplastic changes in the myeloid and erythroid precursor cells.

Patient's blood sample was sent to Obafemi Awolowo University Teaching Hospital (OAUTH), Ile-Ife, Nigeria, for cytogenetic analysis (Karyotyping) which was reported as negative for the Philadelphia chromosome. Patient's blood sample was also sent to Safety Molecular Pathology Laboratory in Enugu, Enugu State, Nigeria for quantification of bcr-abl transcripts. The result showed low levels of Bcr-Abl transcripts ($<10^4$). Other investigations carried out in the patient included serum urea and electrolytes, liver function tests, blood culture and abdominal ultrasound.

She was transfused with 2 units of fresh whole blood (due to non availability of Cold centrifuge for preparation of blood products) administered with Frusemide 40mg stat intravenously. Patient was then commenced on Allopurinol 100mg thrice daily orally, Hydroxycarbamide (Hydroxyurea) 500mg twice daily p.o., and oral liquid morphine 5mg 4 hourly. She also had Augmentin 625mg p.o. twice daily and Ciprofloxacin 500mg p.o. twice daily. Her full blood count (FBC) was monitored twice weekly during admission and following good response to the Hydroxycarbamidetherapy with reduction in WBC count to $12.0 \times 10^9/L$, PCV increase to 35% and platelet count of $125.0 \times 10^9/L$. She was discharged 6 weeks later to be followed up subsequently in the Haematology Clinic of the Hospital.

However, she was readmitted 2 weeks after discharge in the Accident and Emergency (A&E)Unit of the U.I.T.H. Ilorin with fever, severe anaemia and bleeding from the gum and nostrils. A full blood count was done which showed PCV of 10%, WBC count of $54.7 \times 10^9/L$, platelet count of $33.0 \times 10^9/L$ with presence of Myeloblasts $> 20\%$ and other myeloid cells in circulation all showing dysplastic features. An assessment of aCML in blastic transformation was made and patient was transfused with 3 units of fresh whole blood and commenced on AML- type induction chemotherapy regimen with I.V Cyclophosphamide, Ara-C, Vincristine and oral Prednisolone with allopurinol added to the treatment regimen. The

patient's condition deteriorated despite chemotherapy and she died on the third day of admission.

Results

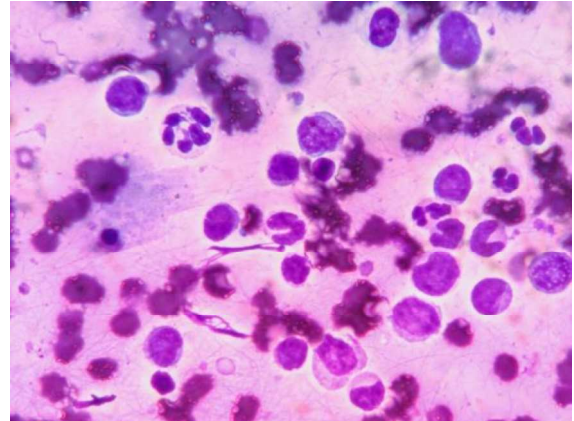


Figure 1: Peripheral blood film of patient at diagnosis (x100 magnification). Showed Myeloid cells at various stages of maturation with features of dysgranulopoiesis

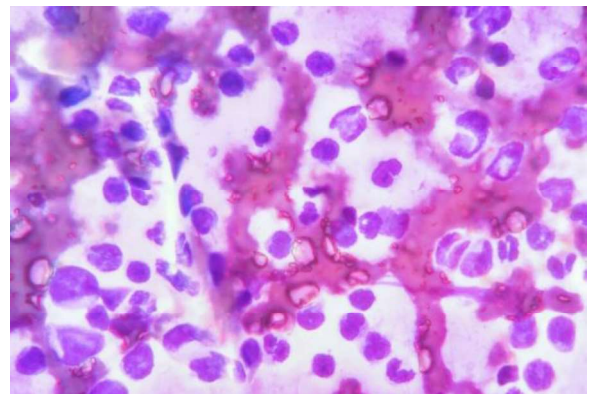


Figure 2: Bone marrow aspiration slide at diagnosis (x100 magnification). Shows myeloid hyperplasia with dysgranulopoiesis

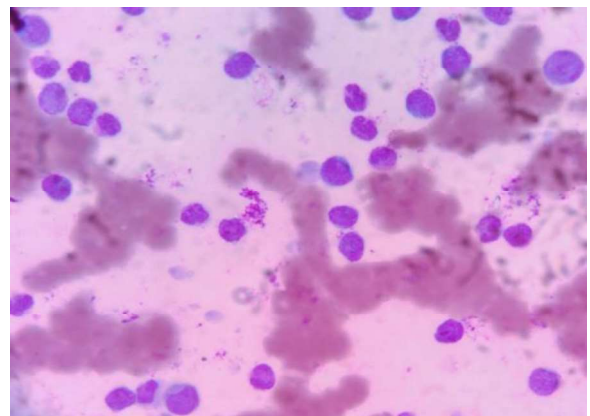


Figure 3: Peripheral blood film of patient when readmitted in blastic transformation (x100 magnification). Shows leucocytosis, increased blasts and thrombocytopenia

Discussion

Atypical CML was first described as a subtype of CML, but the 1994 FAB classification of the Myeloproliferative disorders recognized aCML as a separate clinical entity⁴. The aCML lacks the classical Philadelphia chromosome, t(9;22)(q34,p11), which is found in the regular CML. Although, other chromosomal abnormalities have been described in aCML, these are non specific and are not pathognomonic of the disease^{8,9,10}.

The hallmark for the diagnosis of aCML is the granulocytic hyperplasia with dysplastic features in the bone marrow, and the obvious dysplastic changes in the circulating immature granulocytes of about 10-20%, little or no monocytosis and basophilia. There could also be dysplastic changes in the erythroid precursors in the bone marrow^{4,5}. Our findings of increased number of circulating myeloid cells at various stages of differentiation showing dysplastic changes in the peripheral blood and bone marrow films of the patient was in agreement with the previous studies which reported dysplastic granulopoiesis as a major feature in their aCML patients^{4,6,11}.

The cytogenetic analysis for the Philadelphia chromosome which was done for this patient was negative and the molecular analysis for the Bcr/Abl transcripts were very low. The lack of Philadelphia chromosome in this patient with the low Bcr/Abl transcripts recorded in our study in addition to the peripheral blood and marrow findings above supported our diagnosis of aCML and corroborated other studies which found absence of Ph chromosome and BCR-ABL gene in their aCML patients^{7,8,11}. Several other chromosomal abnormalities such as trisomy 8, trisomy 13, deletion of 12q or 20q11, t(5;10) translocation with expression of PDGFR-B/H4 gene have been reported to be associated with aCML by previous studies among others^{8,11,16,17}. In the present study, there was no screening for any other chromosomal abnormalities which had been reported due to lack of facility for such in the country.

Patients with aCML lack the Ph chromosome and as such do not show good response to the available Tyrosine kinase inhibitors like Imatinib and Dasatinib

which are targeted therapeutic drugs for the Ph + CML. Some studies which tried the Tyrosine kinase inhibitors in their aCML patients reported very poor response and outcome^{13, 14,18}, so conventional cytoreductive chemotherapy with Hydroxyurea or Busulphan had been used for treatment. In our study, Hydroxycarbamide was used for treating the patient who showed significant response to the drug initially but later became refractory with increased blasts, severe anaemia, increasing WBC count and thrombocytopenia which were indicative of a blastic transformation to acute leukaemia within 2 weeks of discharge from hospital. The outcome in aCML patients had been reported to be poor when compared with the Ph + CML. aCML was reported to progress more rapidly to acute leukaemia in up to 40% of patients with a median survival of less than 20 months when compared with median survival time of 5-10 years in the Ph + CML^{7,11}. The survival time from diagnosis to death in our patient was about 8 weeks which was in agreement with other previous studies. Hernandez et al¹⁹ in their study of 11 patients with aCML reported poor response to therapy and a short survival outcome. In younger patients who are diagnosed in early disease, aggressive chemotherapy followed by Bone marrow transplantation has been recommended to improve the survival outcome in such patients^{13,20}. There was no facility in our centre for bone marrow transplantation; otherwise she could have been a good candidate for the procedure. This may have given the patient a better survival outcome.

Conclusion

aCML is an uncommon disease without a recognized cytogenetic marker. It exhibits a mixture of myeloproliferative and myelodysplastic features with a poor outcome. Although it is said to be rare, in our environment where there is paucity of diagnostic tools and limited resources, many cases may have been missed and diagnosed as CML. Thus, there is need for vigilance and thorough screening of perceived CML patients so as not to pass cases of aCML as CML, more so in the face of obvious limitations in carrying out cytogenetic analysis for the Philadelphia chromosome and other chromosomal abnormalities in many centres across the country. Also, the need for improved diagnostic facilities in our tertiary health institutions in the country cannot be overemphasized if we must

achieve proper diagnosis and characterization of cases of aCML as these will to a large extent influence the treatment and prognosis of such cases.

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