

FAMILIAL CHRONIC MYELOCYTIC LEUKEMIA: THE OCCURRENCE IN FIRST COUSINS IN JOS, NORTH CENTRAL NIGERIA

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ABSTRACT

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Introduction: Chronic myeloid leukemia is a leukemic myeloproliferative disorder that is rarely diagnosed in members of the same family. **Aim:** We report the occurrence of chronic myeloid leukemia in male first cousins in Jos. **Cases report:** Two cousins 37 years and 31 years old were referred to our department for leucocytosis in the first patient and priapism and leucocytosis in the second. Full blood count and bone marrow aspiration cytology in both cases revealed granulocytic leucocytosis with all the stages of myeloid maturation in peripheral blood and marrow myeloid hyperplasia in keeping with chronic myeloid leukemia. Treatment with tyrosine kinase inhibitor (TKI) was delayed in both, due to financial constraints for transportation to the treatment center in Nigeria. Cytoreduction with hydroxyurea was the initial treatment instituted. Even with the eventual commencement of imatinib mesylate, the outcome was still poor in the second patient who transformed and died within one year. **Conclusion:** Chronic myeloid leukemia has occurred in family members in our environment.

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Introduction

Chronic myelocytic leukemia (CML), one of the leukemic myeloid neoplasms, is characterized by anemia, extreme granulocytosis, granulocytic immaturity, basophilia, and often thrombocytosis and splenomegaly.¹ Indolent proliferation of myeloid cells in the marrow, spillage into the circulation and organ infiltration is the typical trend of chronic myelocytic leukemia. The typical cytogenetic property of CML is the reciprocal translocation between the telomere of the long arms of chromosomes 9 and 22, described as the Philadelphia chromosome.¹

The evidence linking ionizing radiation to increase in the incidence of CML has been

established among irradiated patients with ankylosing spondylosis, women with uterine cervical cancers and the Japanese survivors of atomic bomb blasts.^{1,2} Chemical leukemogenesis has not linked to occurrences of CML, but to acute myeloid leukemia except topoisomerase II inhibitors known to induce translocation between chromosomes 9 and 22 (t9,22).¹ Human leucocyte antigens; HLA CW3 and CW4 common in CML patients may be markers for susceptibility.¹

CML occurrence is very infrequent in family members and only a few cases have been documented globally. Although rare, few cases of nonleukemic myeloproliferative disorders occurring in members of the same

family have been documented.³ The first familial multiple cases of CML was reported in identical twins by Tokuhata and co-workers in 1968.⁴ Lardi et al (1994) reported chronic myelocytic leukemia-like syndrome among three Saudi siblings in their early infancy.⁵ We are not aware of any report of familial occurrences of CML in our setting. We report a familial occurrence of chronic myelocytic leukemia in two male first cousins in Jos, North Central Nigeria. The ethical clearance for this case report was obtained from the ethics committee of the Jos University Teaching Hospital, Jos, Nigeria. Consent was obtained from the first patient before the report was embarked on.

Aims: This is to report the occurrence, and raise the consciousness of practitioners to the possibility of CML in family members of patients diagnosed with CML.

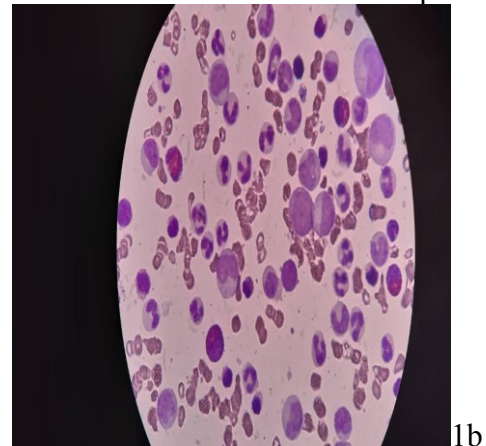
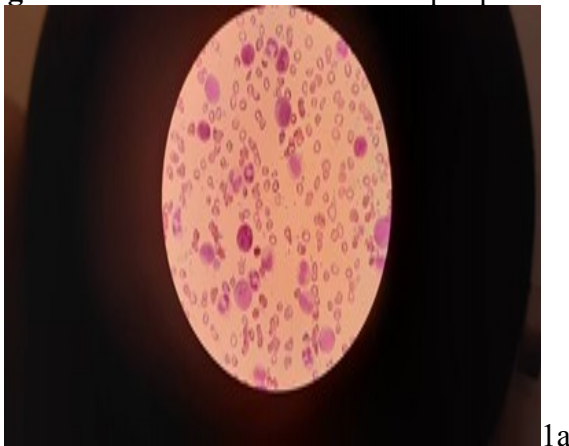
First Case Report: P D, a 38-year-old single male teacher presented four years ago (2015) in the department of hematology and blood transfusion on account of leucocytosis detected on workup investigations in the family medicine department, Jos University Teaching Hospital. The presenting features were progressive left-sided upper abdominal quadrant pain associated with distension,

dragging sensation and easy satiety of three months duration. He also had fever and significant weight loss over a month prior to presentation. There were no associated bone pains, bleeding from orifices, pruritus or subcutaneous swellings. There were no contributory significant symptoms on systemic review. No history of previous illness warranting hospitalization or blood transfusion neither had there been any similar ill health in any member of the family.

Examination revealed a young man in no obvious distress; mildly pale with bilateral pedal edema up to the ankles and no peripheral lymphadenopathy. The other positive clinical sign found was massive splenomegaly extending into the right iliac fossa. Other systemic examination did not elicit any other features.

A complete blood count and bone marrow aspiration of the patient using standard methods were; packed cell volume (PCV) of 0.25 (normocytic, normochromic), total white blood cell count (WBC) $102.0 \times 10^9/L$ (N=65%, L=01%, M=03%, E=02%, B=08%, Metamyelocyte=04%, myelocyte=04%, promyelocyte=10% and myeloblast=04%) and platelet count of $820.0 \times 10^9/L$.

Figure 1: Pictures of interest from peripheral blood and marrow films of the first patient



Peripheral blood film at diagnosis

Bone marrow aspiration cytology revealed a hypercellular marrow with myeloid infiltration at various stages of maturation. Marrow eosinophils and basophils constituted 16% and myeloblasts and promyelocyte; 08% of non-erythroid marrow nucleated cells.

Bone marrow film at diagnosis

A diagnosis of chronic myelocytic leukemia in chronic phase was made. His electrolytes, urea, creatinine and uric acid were within normal limits as well as serum liver enzymes and albumin levels. He was screened negative for markers of hepatitis C and B

viruses and the human immunodeficiency virus.

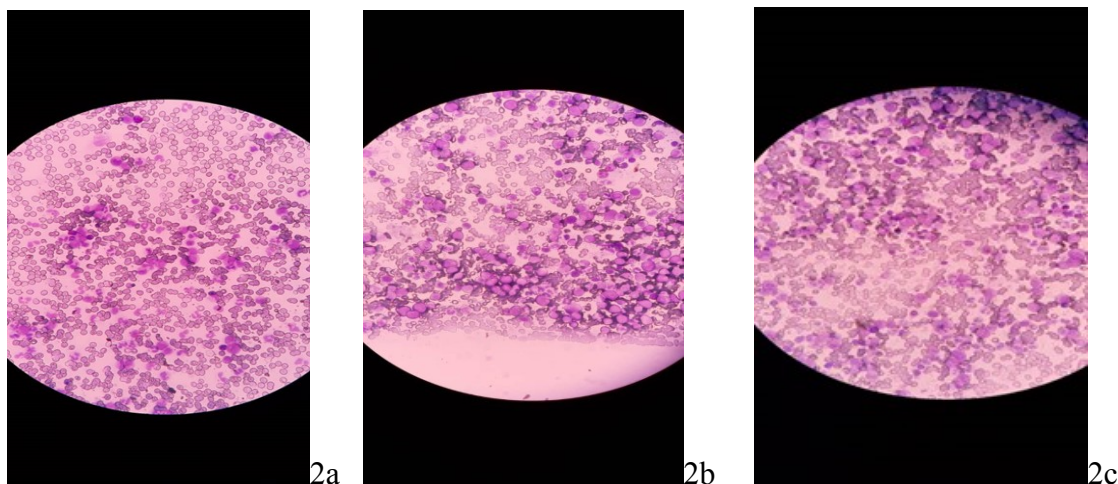
He was counseled on the disease, treatment options available and complications as well as a possible outcome. He declined referral to another center for cytogenetic study and possible commencement on tyrosine kinase inhibitor. He was commenced on hydroxyurea 2000mg in two divided doses and allopurinol 300mg daily. At the sixth week of therapy, the patient returned to chronic phase with a PCV of 0.22, total WBC of $60.0 \times 10^9/L$ and Platelet count of $900.0 \times 10^9/L$. He was again counseled for review in another facility with capacity for cytogenetic study. At the thirteenth week of treatment, the patient failed to have a complete blood count done for financial constraints but had visited the referral center where he was evaluated for Philadelphia chromosome and commenced on imatinib mesylate. He has remained in the remission for four years.

Second Case Report: C. C is a thirty-one-year-old applicant referred to us in 2015 from a nearby University Teaching Hospital where he had penile surgical intervention to

relieve priapism of thirteen hours duration. The surgical procedure necessitated the transfusion of a unit of blood while in the referring hospital. The referral was necessitated by the discovery of leucocytosis at complete blood count did postoperatively for the patient. He had two episodes of epistaxis within one month prior to presentation associated with drenching night sweats and weight loss. No associated bone pains, fever, pruritus or subcutaneous swellings. There were no additional significant systemic symptoms. He was not a known diabetic, hypertensive or sickle cell disease nor was he on any medications. He took both locally brewed and industrial bottled alcohol for eight years but never smoke nicotine. When examined, he was in no distress, not pale, afebrile, no peripheral lymphadenopathy or pedal edema. The abdomen was full non-tender; the liver was down 4cm and smooth while the spleen was not palpable.

At complete blood count; packed cell volume was 0.36, total WBC; $350.0 \times 10^9/L$ and platelet count $300.0 \times 10^9/L$.

Figure 2: Pictures of interest from peripheral blood and marrow films of the second patient



Peripheral blood at Diagnosis Bone marrow at Diagnosis peripheral blood at transformation

Bone marrow aspiration cytology was hypercellular with myeloid cells at various stages of maturation infiltrating the bone marrow. The marrow eosinophils and basophils accounted for 13% while myeloblasts and promyelocytes constituted 8% of marrow non-erythroid cells. The diagnosis

of CML in chronic phase was made. The serum electrolytes, urea, creatinine, uric acid, and liver enzymes levels were within normal limits. Hepatitis B and C and HIV screening were all non-reactive.

He was also counseled on the disease, treatment options available and complications

as well as the possible outcome. He also repeatedly declined referral to another center for cytogenetic study and possible commencement on tyrosine kinase inhibitor. He was commenced on hydroxyurea 2000mg in two divided doses and allopurinol 300mg daily. At a review, at the sixth week on treatment, significant cytoreduction was achieved with no blasts in the peripheral circulation. He was still counseled and again referred for cytogenetic study and possible commencement of targeted therapy. Hydroxyurea was reduced to 1000mg in two divided doses to continue with 300mg allopurinol daily. A review at the eighteenth week of treatment revealed the patient had accelerated with a PCV of 0.23, platelet; $80.0 \times 10^9/L$, total WBC; $48.0 \times 10^9/L$ with blasts and promyelocytes of 16% associated with weakness, fever and cough while on imatinib mesylate obtained from the referral center. Further CBC at review, thirteen weeks later; PCV=0.19, total WBC = $450.0 \times 10^9/L$ with myeloblasts and promyelocytes accounting for 48% and a platelet count of $44.0 \times 10^9/L$ associated with cough and fever. The diagnosis of transformed CML was entertained and the patient stabilized and commenced remission induction on daunorubicin $50mg/M^2$ days 1-3 and cytosine arabinoside $100mg/M^2$ days 1-7. He had four units of fresh whole blood transfused in the course of remission induction along with intravenous antibiotics. Fever and cough resolved over 10 days. Complete blood count on day fourteen showed a PCV of 0.27, total WBC of $3.0 \times 10^9/L$ and platelet count; $82.0 \times 10^9/L$. He was assessed to be in remission and discharged to see in hematology outpatient clinic in two weeks. The patient could not come to the clinic as appointed and the team was informed of his death in another hospital one month later through his first cousin being managed for the same illness.

Discussion: The occurrence of CML in these two first male cousins concurred with earlier local and international observed greater disease affectation among the male than prevalent in the opposite sex.^{1,6} Reported familial presentations with CML are few, with a 1968 description in a Japan's identical twins

and a 1994 report of CML like syndrome among three Saudi siblings in their infancy.^{3,4} The diagnosis of CML in our related patients confirmed and adds to the few reported cases of this disease in family members. The reported non-significant aggregation of CML in family members deduced from a Sweden study of high-quality registry data may be the same in our setting despite these two cases. This suggests the need for the setting up of a Nigerian national leukemia registry which will serve as a local large data source for future studies.⁷ The diagnosis of CML in our patients who shared the same age bracket (38 and 31 years respectively) suggests possibly inherited similar genetic abnormality and exposure to similar environmental factors. Our patient might have also harbour different cytogenetic abnormalities as was the reported case of familial occurrence of CML in a 45 year old sister and her 50 year old brother.⁸ Survey of cytogenetic abnormalities among close family members of patients with leukaemias particularly CML may yield useful data for follow-up surveillance and early disease detection, counseling, treatment and better quality of life.

Chronic myeloid leukemia (CML) is characterized by clonal proliferation and accumulation of myeloid cells in sequential stages of maturation detectable at the haematologic analysis of the peripheral blood sample. Haematologic investigations of patients who present with non-specific symptoms such as weakness or fatigue, night sweats, and weight loss, may reveal an underlying leukemic myeloproliferative disease in symptomatic and in some instances asymptomatic patients.⁹ Significant fever with night sweats, weakness, weight loss were among the symptoms seen in our patients. Left upper abdominal quadrant pain, dragging sensation, abdominal distension and early satiety in our first patient are recognised clinical features associated with massive splenomegaly.² Epistaxis and priapism that occurred in the second patient may be due to vascular congestion, occasioned by Hyperviscosity.¹⁰ The investigations of patients presenting with priapism should always

include a full blood count and examination of a well prepared peripheral blood film which may reveal haematologic causes such as leukemia and non leukemic myeloproliferative disorders including CML.^{11,12} Thrombocytopenia, a recognized platelet defect in CML, may explain the recurrent epistaxis that form part of our patient's presentation.¹³ The absence of splenomegaly in our second patient concurred with the recorded absent of splenomegaly in a minority of patients diagnosed with CML.^{9,14}

The diagnosis of chronic myeloid leukemia in the two cousins seen in our facility in 2015 was based on full blood count that demonstrated matured high granulocytic leucocytosis in the peripheral blood and hypercellular bone marrow with the full spectrum of granulocytic maturation on cytology, confirmed by the demonstration of BCR-ABL fusion mutation in both.^{15,16} The cardinal haematologic features of CML in the chronic phase are; leucocytosis with mean WBC of $100.0 \times 10^9/L$, <15% blasts, <20% basophils, <30% blasts and promyelocytes in the peripheral blood and marrow and platelet count of $\geq 100.0 \times 10^9/L$.¹⁷ The two familial patients being reported both had full blood counts and marrow evaluations that were in keeping with haematologic findings in the chronic phase of CML. The haematologic parameters in our patients are also comparable to leucocytosis with basophilia and immature granulocytes mainly metamyelocytes, myelocytes, promyelocytes, and occasional myeloblasts: features of CML described by Baccharani and colleagues.¹⁸ Demonstration of Philadelphia positivity in our patients was done in another center with facility of cytogenetic studies, enrolment of eligible patients for TKIs therapy. This concurred with Van-Etten and co-workers, who analyzed the presence of Philadelphia chromosome detection in a majority of patients with chronic myeloid leukaemia.¹⁹ Identification of a cytogenetic abnormality unique to cancer was first observed in chronic myeloid leukemia. This led to the identification of a BCR-ABL fusion gene involving chromosomes 9 and 22 in a reciprocal translocation, fusion gene product with dysregulated tyrosine kinase-like activity

and eventually the development of TKIs, currently the standard treatment and monitoring of disease course.¹⁵

Leukemia carries an important burden of morbidity and mortality in Nigeria with CML accounting for 27.7% of all leukemia cases diagnosed.²⁰ The TKIs treatment site in Obafemi Awolowo University Teaching Hospital, Ile-Ife, South-Western Nigeria has been providing free/subsidized investigations and free imatinib mesylate to patients for the treatment of those who are Ph-positive CML in chronic phase.²¹ Hydroxyurea and allopurinol were used to initiate cytoreduction and prevent hyperuricemia respectively.²² This was necessary as the confirmation of the Philadelphia chromosome in the two patients was not immediately available and affordable, in our center, in the face of high WBC counts at diagnosis. Priapism that occurred in our second patients also necessitated the institution of hydroxyurea which achieved cytoreduction and prevented further recurrence. While hydroxyurea benefits for cytoreduction with no influence on disease course, the TKI imatinib mesylate, has been shown to have superior response rate compared to interferon-alpha and cytarabine as initial treatment for newly diagnosed CML in chronic phase.^{23,24} This realization motivated the repeated counseling and eventual referral of our two cousins to the only center in Nigeria where both were confirmed and enrolled in treatment.

We could not ascertain the adherence and compliance of our patients to their treatment and follow-up management at the referral center since they were subsequently not regular at our scheduled hematology clinic. Buslphan, like hydroxyurea, only achieve cell count reduction with the likelihood of complications without any effects on disease course, is no longer use in the treatment of CML.²¹ Stem cell transplantation where available is currently reserved for selected cases of chronic myeloid leukemia.²⁴ The second of our two cases could have benefited from stem cell transplant if availability, accessibility, and affordability were guaranteed.

Conclusion: We reported the diagnosis of chronic myeloid leukemia in family members in north-central Nigeria, highlighting the challenges of management in a resource-limited setting.

Limitations: The lack of facility for confirmation of CML and financial constraints on the patients' part combined to delay molecular studies and commencement of TKIs in the patients. Recurrent industrial unrest in the health sector is a major impediment to patient follow-up and quality care as the requisite resources are limited to few public tertiary health facilities.

Recommendation: There is a need to build up capacity in more treatment centers for chronic myeloid leukemia care, for ease of access to confirmation, treatment, and follow-up.

Conflict of interest: none declared

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