



## Acute Eosinophilic Leukemia: The Challenges of Management in a Resource Poor Setting

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### Abstract

**Introduction:** The diagnosis of certain subtypes of leukaemia is rarely made and descriptions in the literature are scantily found.

**Aim:** This report aimed to describe a case of acute eosinophilic leukaemia, highlighting the management challenges in Jos.

**Case Report:** A 36-year-old female tailor presented in the emergency and accident unit of the hospital with fever, epistaxis and menorrhagia. She was transfused for anaemia before presentation. She was bleeding from the nose, pale and febrile. Full blood count revealed severe anaemia, thrombocytopenia and eosinophilic leucocytosis. Bone marrow aspiration (BMA) cytology showed myeloid hyperplasia with eosinophilic myeloblasts. Supportive hydration, blood transfusion, ant-microbial agents and allopurinol were administered. The patient was counselled and Daunorubicin and Cytosine arabinoside (DA) regimen was commenced. Evaluation on days 14 and 28 revealed only improvement in clinical and laboratory features. Induction of remission was embarked upon again with DA regimen. On day 14 of re-induction, the haemogram remained essentially the same. She was maintained on the regimen for eight cycles when symptoms of fever and mucosal bleeding (gum) resumed, accompanied by raised WBC, severe thrombocytopenia, neutropenia and anaemia. She was on intravenous saline, fresh whole blood transfusion and antibiotic. Drugs regimen was changed to cyclophosphamide, vincristine, methotrexate and prednisolone.

**Conclusion:** Rare forms of leukaemia when seen in the developing nations are faced with management limitations.

**Keywords:** Eosinophilic; Leukaemia; Management; Challenges

### Introduction

The myelomonocytic leukaemia, a subtype of myeloblastic leukaemia, includes a rare variant characterised by the presence of eosinophilic intracytoplasmic granules designated Acute Myelomonocytic leukaemia; eosinophilic variant (AML-M<sub>4Eo</sub>) [1,2]. Eosinophilia is generally classified into reactive, clonal or unexplained with eosinophilic leukaemia presenting with absolute eosinophil count of  $>1.5 \times 10^9/l$  or 50 to 80% eosinophilic cells in blood and marrow [3,4]. Acute myelomonocytic leukaemia

accounts for 5 to 20% of acute myeloblastic leukaemia cases; affecting more males than females in the older age groups [5].

Weinger and colleagues (1975) recognised the vital role of clinical presentation and peripheral blood morphology in the evaluation of acute eosinophilic leukaemia. They also showed that the application of electron microscopy was able to identify abnormality to the level of promyelocyte while histochemistry

provided the evidence of true eosinophils [6]. Bianco et al. documented the finding of blast cells positive for cyanide resistant peroxidase specific for eosinophils in all stages of maturation while chloroacetate esterase reaction was aberrant [7]. Kueck et al. (1991), concluded that eosinophilic leukaemia is a myeloproliferative disease distinct from the hypereosinophilic syndrome. They demonstrated trisomy 8 and 21, morphologic, cytochemical, ultrastructural granular abnormalities and nuclear cytoplasmic asynchrony with a clinical course similar to myeloproliferative disease and not a hypereosinophilic syndrome [8]. The treatment of acute eosinophilic leukaemia is similar to other acute myeloblastic leukaemias except subtype ALM-M3 [5].

The acute eosinophilic leukaemia has not been fully understood with only a few reported cases available in the literature. We are not aware of any case described in our setting, where leukaemias generally are under documented and challenging to manage due to limited resources. We report the first case of acute eosinophilic leukaemia seen in the Jos University Teaching Hospital, in Jos city of Plateau State, Nigeria, in 2015 highlighting the prevailing management constrains.

### Case Report

LD is a 36-year-old female tailor who resided in Jos, the capital city of Plateau State, Nigeria. She presented in the emergency and accident unit of the hospital with complaints of recurrent, progressive fever and epistaxis of four weeks and one-week duration respectively and menorrhagia. There was associated progressive weakness and paleness of the skin and mucosae which warranted transfusion of blood in a primary healthcare centre before the presentation. There was no bone pain, subcutaneous or abdominal swelling or pruritus.

The patient had episodes of a dry cough associated with difficulty in breathing, no chest pain or haemoptysis. She had anorexia; however, there was no vomiting, malaena stool or a change in bowel habit. No haematuria, dysuria or any other urinary symptoms. No associated headache, blurred vision, seizures or loss of consciousness. Last menstrual flow which occurred two weeks prior to onset of illness was somewhat increased and prolonged, no prior vaginal discharge or post coital bleeds. She was a mother of three who's last child birth was two years in a monogamous setting. There was no history of smoking nicotine, alcohol intake or multiple sexual partners. The patient past medical history was

unremarkable, not a known diabetic, hypertensive or has any bleeding tendency. She was treated with antibiotics, antipyretics, analgesics including non-steroidal anti-inflammatory agents, antimalarial and six units of whole blood transfused before presenting to us.

Examination revealed an acutely ill looking young woman with a surface area of approximately 1 M<sup>2</sup>, bleeding from the nose, febrile (T 39.2°C), dehydrated, pale, anicteric, and had blood stained buccal mucosa, no peripheral lymphadenopathy or pedal oedema. Respiratory breath sounds were vesicular with no crepitation. The pulse rate was 98 beats per minutes, blood pressure of 110/70 mmHg and a normal heart sound only. Her abdomen was flat, non-tender, no intra-abdominal masses or ascites. The musculoskeletal system showed no loss of function or bone tenderness. She was conscious and oriented.

A manual full blood count revealed a packed cell volume (PCV) of 0.19, total white blood cells (WBC); 218.0 X 10<sup>9</sup>/L and platelet count of 16.0 x 10<sup>9</sup>/L. Red blood cell morphology was essentially normocytic, normochromic. The differential white cells count was neutrophils (N); 2%, lymphocytes (L); 3%, eosinophils (E); 6%, eosinophilic myelomonocytes; 63% myeloblasts; 26% (Table 1). The absolute count of white cells with eosinophilic granulation was 137.3 x 10<sup>9</sup>/L. Thrombocytopenia was also confirmed at blood film examination (Figure 1).

Bone marrow aspiration (BMA) cytology showed hypercellularity with an M:E ratio of 27:1. Erythropoiesis was suppressed but normoblastic. The marrow was infiltrated with myeloblasts and myelomonocytes, containing intracytoplasmic eosinophilic granules accounting for 64% of non-erythroid marrow nucleated cells. Megakaryopoiesis was severely suppressed while lymphocytes and plasma cells were within normal limits (Figure 2). Based on peripheral leucytosis and marrow myeloblasts (>20%) and eosinophilic myelomonocytic cells constituting 64% of non-erythroid marrow nucleated cells, a diagnosis of AML-M4Eo was made.

On further investigation, urea was 8.6 mmol/L while creatinine, uric acid, electrolytes and random blood glucose were within the normal limits. Serum protein, bilirubin and liver enzymes were also within the normal ranges. Viral screen for hepatitis B and C and the human immunodeficiency virus (HIV) were all negative. Blood cultures did not yield any bacterial isolate. The

abdominal ultra sound scan showed no enlargement of any organs or a retroperitoneal tumour. Her ABO and Rh blood groups were B Rh D positive.

The patient was admitted from emergency into the female medical ward of the hospital for further management. Other investigations to rule out hypereosinophilic syndrome and lymphoproliferative disorders associated with eosinophilia were not done; cytochemistry, flow cytometry and cytogenetic studies such as translocation t(16;16), inv(16) which would have confirmed de-novo AML-M4Eo or t(9;22) in transformed chronic myelocytic leukaemia, immunohistochemistry for myeloid markers (CD13, CD14, CD33) were not possible due to the poor facility in our centre [9]. Financial constrains prevented our patient from accessing these services at other referral centres.

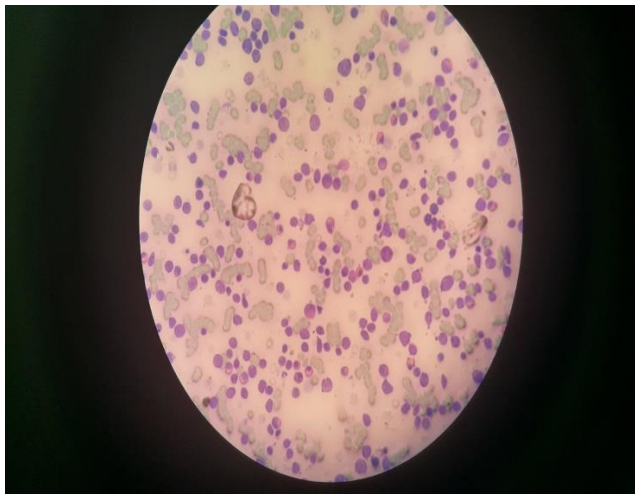
The performance status of the patient was limited to self-care and restricted to bed for more than 50% of the time (ECOG/WHO Grade 3) [10]. The patient was counselled on the implications of the diagnosis, management options available and expected outcome including drug side effects. Supportive treatment,

including intravenous rehydration, allopurinol, antibiotics and transfusion of safe, compatible fresh whole blood where administered.

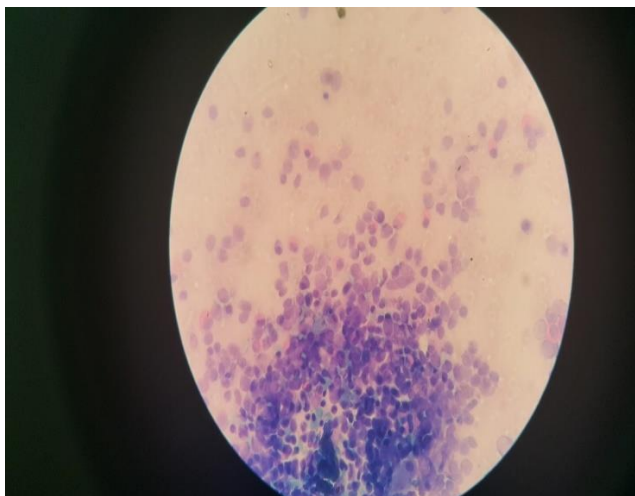
Definitive intervention aimed at remission induction with Daunorubicin 25 mg/m<sup>2</sup> daily for three days and cytosine arabinoside 100 mg/m<sup>2</sup> daily for seven days were administered [9]. She was also transfused an additional two units of fresh compatible blood while in the hospital for worsening anaemia and thrombocytopenia. Six days after commencement of remission induction, temperature fell to 36.8°C accompanied by improvement in the patient's feeling of wellbeing. A repeat FBC on the eighth day was; PCV 0.24, WBC count of 54.0 x 10<sup>9</sup>/L with 73% immature and 27% matured eosinophils, and a platelet count of 22.0 x 10<sup>9</sup>/L (Table 1) with no mucosal bleeds. Further evaluation on day 14 revealed a stable patient with improved appetite. There were no more fever, epistaxis or bone pains. The PCV was 0.23, WBC 9.6 x 10<sup>9</sup>/L (N; 7%, Eo; 73%, Eo myelomonocytes; 20%) and platelet of 72.0 x 10<sup>9</sup>/L (Table 1). The assessment of clinical improvement was made, and the patient was discharged to follow up at the outpatient unit of the department in two weeks.

**Table 1:** Haematologic parameters of patient at diagnosis and through the treatment course.

Parameters	At diagnosis	First remission induction			Second remission induction		
		Day 8	Day 14	Day 28	Day 14	Day 28	8 Months
PCV	0.19	0.24	0.23	0.26	0.26	0.31	0.16
WBC (x10 <sup>9</sup> /L)	218	54	9.6	7.2	7.2	5.9	28
Neutrophils (%)	2	0	7	12	12	55	2
Lymphocytes (%)	3	0	0	0	0	0	0
Monocytes (%)	0	0	0	2	3	11	0
Eosinophils (%)	6	27	59	54	63	14	0
Basophils (%)	0	0	0	0	0	0	0
Eo Myelomono (%)	63	73	34	32	22	20	0
Myeloblasts (%)	26	0	0	0	0	0	98
Platelets (10 <sup>9</sup> /L)	16	22	72	110	162	220	12
Eo Myelomono: Eosinophilic myelomonocytic cells							



**Figure 1:** Patient's peripheral blood film at diagnosis showing eosinophilic leucocytosis (x40).

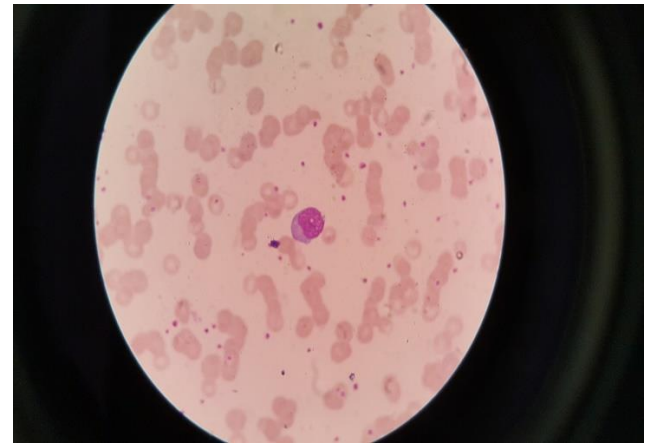


**Figure 2:** Patient's Bone marrow Film showing a hypercellular fragments with immature eosinophils and myeloblasts (x 40).

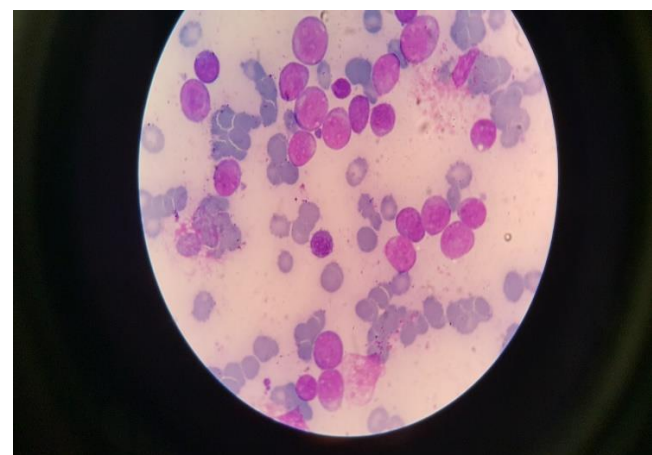
At the clinic follow up visit on the 28<sup>th</sup> day, she had no symptoms and felt a remarkable physical improvement in wellbeing. Her PCV=0.26, WBC=7.2 x 10<sup>9</sup>/L (N; 12%, Eo; 64%, Eo myelomonocytes; 22% and Monocytes; 2%) and platelet count of 110.0 x 10<sup>9</sup>/L (Table 1). She was further administered 25mg/m<sup>2</sup> of daunorubicin and cytosine arabinoside 100mg/m<sup>2</sup> days 1-3 and 1-7 respectively for re-induction of remission in the outpatient clinic. On day 14 of second remission induction, the haemogram remained essentially the same except a further rise in platelet count to 162.0 x

10<sup>9</sup>/L. On day 28<sup>th</sup>, the PCV was 0.31, WBC; 5.9 x 10<sup>9</sup>/L (N; 55%, Eos; 14%, Eo myelomonocytes; 20% and Monocytes; 11%) and platelet count 220.0 x 10<sup>9</sup>/L (Table1 and Figure 3).

She was maintained on the DA regimen monthly for eight cycles and the remained essentially the same. Fever and mucosal bleeding (gum) returned at the ninth visit, accompanied by raised WBC; 28.0 X 10<sup>9</sup>/L (predominantly of myeloblasts with scanty eosinophilic granulation), thrombocytopenia (12.0 x 10<sup>9</sup>/L) and severe anaemia (PCV=0.16) (Table 1 and Figure 4).



**Figure 3:** Patient's blood film on day 28 of second remission induction, showing Thrombocytosis (x100 oil immersion).



**Figure 4:** Patient's blood film at clinical relapse showing myeloblasts with scanty eosinophilic granulation (x100 oil immersion).

She was admitted into the ward and supported with intravenous saline, fresh whole blood transfusion of three units, allopurinol 300 mg daily and antibiotic cover. Sepsis screening did not yield any microbial growth. Drugs regimen was changed to the second line; cyclophosphamide 650 mg/m<sup>2</sup> day 1, vincristine 2 mg/m<sup>2</sup> day 1, cytosine arabinoside 100 mg/m<sup>2</sup> day 1-7 and prednisolone 40 mg/m<sup>2</sup> day 1-7 (COAP) [9]. On the third day, she developed a severe headache, became unconscious and died before commencement of the COAP as she could not raise funds to procure the drugs. Her care giver declined consent for an autopsy.

## Discussion

Acute as compared to chronic leukaemia is not unusual in those aged 40 years and below [7]. Although eosinophilic leukaemias are very rare; this case described the second eosinophilic leukaemic disease diagnosed in this city within four years, the first being a chronic variant [9]. The diagnosis of both acute and chronic eosinophilic leukaemias calls for increased awareness among local clinicians, high index of suspicion and careful, deliberate search for these globally rare diseases that may subtly present in our setting. Although this patient's presentation is similar to the described chronic form, by geographic location and presence of fever, the absence of bone pains and splenomegaly, it differs by the absence of lymphadenopathy, the presence of severe anaemia and thrombocytopenia warranting blood transfusion and the short duration of illness [11]. Despite the observed peculiarities, it should be noted that the clinical features observed in this patient at presentation constituted in part, the described symptoms and signs of leukaemias in general [9,11]. Late presentation of our patient to appropriate health care facility that could evaluate, diagnose and treat the disease early is a significant management challenge in under developed countries. There is need to educate and train health care providers at various care levels to recognise both clinical and laboratory presentations that point to haematologic neoplasms, for referral and to avoid empirical treatment of every anaemic patient with blood and blood products.

Peripheral myeloblasts with eosinophilic granules in high count resulted from marrow proliferation, maturation arrest, accumulation and spillage into the blood circulation, typical of leukaemia [9]. The marrow impact is the suppression of haemopoiesis; erythropoiesis, thrombopoiesis and normal

granulopoiesis which may largely explain the attendant anaemia, thrombocytopenia and neutropenia documented in this patient [12]. Another major challenge encountered was the limitation of our diagnostic investigations to the examinations of Romanovsky stained films of peripheral blood and marrow aspirate. Despite earlier reports on the usefulness of electron microscopy, immunohistochemistry (CD13, CD14, CD33 and CD64), cytogenetics (inv (16), t(6;9), t(8;21)) and cytochemical reactions (Myeloperoxidase, Sudan black, Non-specific esterase, cyanide resistant peroxidase) in differentiating eosinophilic leukaemia from the hypereosinophilic syndrome, disease characterisation, prediction of clinical course, targeted therapies and assessment of remission; practitioners in underdeveloped and developing nations are compelled to rely mainly on clinical features and morphologic studies [13,14]. Computed tomography (CT) scan and magnetic resonance imaging (MRI), not covered by the National Health Insurance Scheme (NHIS), which could identify early features of central nervous system complications are expensive and infrequently functional in our setting. There is need for a strong government commitment to the provision of appropriate healthcare services to the citizenry. This will reduce medical tourism to nations with better healthcare facilities and help reverse capital flight from Nigeria.

Supportive care for our patient began with patient stabilisation, counselling on the disease, treatment options and possible complications and expected outcome as recommended by earlier writers [5,9]. Patient stabilisation did not go beyond IV fluid rehydration, broad spectrum antibiotic coverage and transfusion of fresh whole blood [5,9]. The transfusion of fresh whole blood, despite the documented attendant complications, to a patient with acute leukaemia in attempt to raise red cell volume and platelet count is still the practice in the centre like ours that lack facility for component preparation [15,16]. The transfusion of apheresis platelet, red cell concentrate and the use of G-CSF have since proven effective for the correction of cytopenia and prevention and or treatment of bleeding, anaemia and treatment of bacterial infections respectively [17,19]. The absence of facilities for blood cells concentration or apheresis posed a great challenge to the management of this patient, implying the same for other cases of leukaemias. The provision of these services is necessary; otherwise even the patients that may be referred to and or diagnosed of leukaemia early

in tertiary hospitals in developing countries stand to benefit little from blood transfusion. Palliative care is another supportive intervention available to patients with leukaemia's in more developed nations [19]. The shortage of palliative care specialist prevented our patient from adequate physical, emotional, cultural, social and spiritual support.

Definitive treatment of patients with acute myeloid leukaemia traditionally aims at remission induction, post-remission intensive therapy and stem cell transplant. The agents for remission induction for acute myeloblastic leukaemia available in our setting are daunorubicin and cytosine-arabioside (DA) as the first-line [9]. The failure of our patient to enter remission on the DA regimen left us with the option of achieving and maintaining leukemic cytoreduction and improvement in normal cell count, as other agents for the re-induction of remission were not available, inaccessible and unaffordable. Increase accessibility to, and the utilisation of precision medicine such as FLT specific tyrosine kinase inhibitors, Bcl-2 family inhibitors and toxin conjugated anti CD-33, not found in our settings, have proven effective in the management of selected patients with AML in the developed world [21].

Acute eosinophilic leukaemia in our patient was a refractory disease that failed to achieve complete remission after the second course of DA [22]. The high poverty level in Nigeria could have prevented our patient from accessing care in other countries with the appropriate facility where alternative treatment modalities might have resulted in improved outcome. Myeloablation and stem cell transplant are combined in technologically advanced countries to achieve cure in the management of patients with AML [23]. The selection of suitable stem cell donors by HLA typing for transplantation of needing patients is available in few centres locally while stem cell transplantation is currently limited to the treatment of sickle haemoglobinopathy. There is a need to advance the healthcare of the patient through collaboration with developed centres to diagnose, classify and treat patients with leukaemia, particularly rare types. Low awareness and acceptance of autopsy among our population as typified by the caregiver to our patient is also an important impediment to the accurate and precise determination of the cause of death and improvement in training and knowledge.

## Conclusion and Recommendation

The diagnosis and management of rare haematologic disorders are hindered by the poor state of healthcare services in our setting. We recommend appropriate investments into the health sector in Nigeria for effective management of leukaemia's in line with the global standard. There is need to train medical specialist in palliative care to properly attend to terminally ill patients.

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