Case Report

Acute Leukemia in A Young Female Adult Presenting for Care in A Resource Constrained Setting

Simakando A. Mwizabi[1], Brian Musuka[1], Celine Mwape[1], Audrey Mulenga[1], Mutale Mweene[1], Catherine Maliko[3], Gamal Maksoud[1], Mwinsa Chimese[2], Mabvuto Zulu[4], Sebastian Chinkoyo[1], Christopher Nyirenda[1]*

[1]The Copperbelt University, School of Medicine, Department of Clinical Sciences, Ndola, Zambia

[2]Ndola Teaching Hospital, Department of Internal Medicine, Ndola, Zambia

[3]Ndola Teaching Hospital, Public Health Nursing, Ndola, Zambia

[4]The Copperbelt University, School of Medicine, Department of Clinical Sciences, Kitwe, Zambia

Abstract:

Background: Acute leukemia is a rare malignant disorder arising from an abnormal proliferation of hematopoietic precursor cells. With advances in the management of leukemia, patients of acute leukemia have high chances of achieving adequate remission and survival. However, due to late presentation, diagnosis and treatment, the disease has significantly contributed to high morbidity and mortality especially in resource limited settings.

Method: A comprehensive history and physical examination was taken, coupled with literature review. Various rationale for each intervention and recommended interventions unavailable in our setting were noted.

Results: Early diagnosis and treatment of leukemia and its complications is a major public health concern for which the general public needs to be educated on. In this case report, material and human resource constraints in our setting may contribute towards the patient's poor clinical outcome.

Conclusion and recommendations: Acute leukemia is a manageable disorder provided the availability of appropriate resources and interventions being implemented early. There is therefore need to equip our health facilities and personnel with resources towards early clinical detection, diagnosis and treatment which measures are essential for successful management and prevention of unwanted complications.

Introduction

Acute Leukemia is a multifaceted disease resulting from deregulation in various pathways due to unregulated cell survival and proliferation [1]. This further results in bone marrow accumulation of malignant blast cells, dysregulation of hemostatic system and immune cell function [2].

Etiology of these cancers is not fully understood; however, viruses, cytotoxic poisons, irradiation and immune suppression play a role [3]. Acute Myeloid leukemia accounts for 20 to 25% of all Acute Leukemia and up to 50% cases in Africa being Acute Myeloid leukemia [4].

Despite a great improvement in the management of leukemia among children with greater than 95% survival at 5years, there is poor prognosis varying from 30 to 75% among patients aged 15 to 30years old [5, 6, 7].

A study involving a 23-year-old female, was conducted at a teaching hospital on the Copper belt province of Zambia. Patient came in as a referral from a local clinic of one of the districts in the province.

This study focused on the presentation, management and prognosis of acute leukemia among patients in the Zambian setting. There is little information on hematological cancers in our communities.

History

History was obtained from both the patient and the care giver. Patient was a F/23 who presented with dark skin patches, gum bleeding, headache and hematuria. Patient was well until 7 days prior to admission when she developed headache and dark patches on her skin.

The headache was temporal in location, progressively worsening and throbbing in nature. It was non-radiating with no known aggravating or relieving factors. It was associated with dizziness and body weakness. There was no history of vomiting, seizures and or blurry vision.

The dark patches on skin were of insidious onset, fast progressing and associated with sores in the mouth. The sores were not painful or pus filled but contained blood and were

located on the inner aspects of both cheeks. The dark patches were painful but not itchy. They were flat and associated with swelling of the legs. There was no swelling of the abdomen.

The bleeding from the mouth started 3 days prior to admission and was estimated to be about 500mls per day but not associated with abdominal pain or vomiting.

Hematuria started 3 days prior to admission. It was total in nature and associated with swelling of the eyes which were worse in the morning and improved during the day. There was no history of abdominal pain, dysuria, urgency, frequency or nocturia.

There was history of loss of weight and appetite, no night sweats and no body hotness. There was a positive history of chest pain located in the sternal region which was throbbing in nature, non-radiating and no known aggravating or relieving factors and positive history of palpitations. No history of cough, difficulties in breathing, orthopnea, paroxysmal nocturnal dyspnea, wheeze or leg swelling.

Her last menstrual period date lasted 4 days, and was not associated with menorrhagia. There was no history of miscarriages or STIs. She was a mother of one child.

Patient had no history of diabetes, hypertension, tuberculosis, asthma, and epilepsy and was HIV negative. There was no other relevant past medical or surgical history. She had no history of radiation exposure, receiving blood or any operations.

Patient was on folic acid from local clinic. However, there was no history of herbal medication usage or any known allergies. There was a report of a similar presentation in the auntie. Patient was a single mother, stopped school in Grade 11 and was unemployed. She did not smoke nor take alcohol.

Differential Listing

1. Bleeding diathesis secondary to Acute Leukaemia with anaemia.
2. Bleeding diathesis secondary to Lymphoma with anaemia.
3. Bleeding diathesis secondary to Disseminated Intravascular Coagulation with anaemia.
4. Bleeding diathesis secondary to Multiple Myeloma with anaemia.
5. Bleeding diathesis secondary to Idiopathic thrombocytopenic purpura.

Physical assessment

Physical assessment revealed ill-looking patient with bleeding gums, spontaneous and regular breathing, respiratory rate of 24 breaths/minute and oxygen saturation of 95% on oxygen via nasal prongs. She had a crusted lesion on the right buccal mucosa measuring about 3cm. She had petechiae on the tongue and the hard palate and, petechiae, ecchymosis and purpura on both the upper and lower limbs.

The Glasgow Coma Scale (GCS) was 14/15. Patient was catheterized and 24hr urine monitoring conducted. Temperature was 36.5^0C, BP was 138/83mmHg, pulse rate was 102 beats/minute and urinalysis was non revealing.

On days 2 and 3 of admission there was active bleeding from the gums with a decreased GCS of 8/15, RBS 10mmol/L and urinalysis was normal, BP=136/86mmHg, Pulse=80bpm,

MAP=109mmHg, SPO_2=99% on oxygen via nasal prong, capillary refill time=2 seconds and respiratory rate=24bmp and temperature=37.5^0C. She however had no lymphadenopathy, no splenomegaly or hepatomegaly or pedal edema. Patient received 1 unit of blood

Results: FBC; Hb 8.5, platelet $98x10^9$ WBC $29x10^9$, Liver function test were normal, peripheral smear=awaited results, Chest X-ray showed a resolving mediastinal mass extending to the right side of the chest. There was a positive occult blood in stool.

Bone marrow aspiration was done; however, results were not available at the time of case presentation as the sample had been sent to another University Teaching Hospital (UTH) for analysis. Other investigation such as kidney sonography (kidney involvement as result of tumor lysis syndrome), lumbar puncture (rule out CNS involvement) and immunophenotyping (to determine the cell lineage) were not conducted.

On day 5: Patient was unconscious, GCS 6/15, intubated and with NG tube inserted. Eyes were open with pupils of about 3mm and not responding to light. Conjunctiva was pale and patient was febrile to touch with a temperature of 38 degrees Celsius, BP 135/83mmHg, pulse 86bpm. IV access was established and 2 units whole blood was given.

Therapeutic Interventions

Whole blood and platelet transfusion, Paracetamol 1g tds po, X-pen 2.4mu qid iv and Metronidazole 500mg tds iv and Allopurinol were administered.

Patient was moved to the medical high dependency unit for critical care. Initiation of chemotherapy awaited peripheral smear results.

Established chemotherapy among adult with confirmed leukemia was adopted from the pediatrics protocol for leukemia; it includes induction, consolidation and long-term maintenance with CNS prophylaxis. Combination therapy has proved to be more effective with drugs used including; vincristine, corticosteroids, anthracycline, cyclophosphamide and daunorubicin [8], while in a well-equipped setting, stem cell transplant could also be done.

Follow-up and outcome

Patient was followed up for a week. Her GCS kept deteriorating and unfortunately, she died before the confirmatory results came back from the UTH.

Discussion

Acute Leukemia is a malignant disorder resulting from the clonal proliferation and abnormal differentiation of hematopoietic precursors of the myeloid or lymphoid lineages. Characterization of the blast-cell population present in the bone marrow and peripheral blood (by morphology, cytochemistry, cytogenetics, and immunophenotyping) enables the clinician to determine whether the patient has acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). This distinction is of considerable importance, since treatment and prognosis differ for the two diseases. Of the two major

subgroups, acute lymphoblastic leukemia is more common in children, while acute myelogenous leukemia predominates in adults.

There are distinct differences between sub-Saharan Africa and the industrialized countries as to the age and gender distributions of the leukemias. In sub-Saharan Africa, incidence of acute lymphoblastic leukemia (ALL) is low (1/100 000/year); the deficit is specifically of common ALL (c-ALL) in children under 5 years of age. T-ALL is the more common form with a peak frequency at 5 to 14 years of age. In the past 12 years, however, c-ALL has been observed with increasing frequency in black children of South Africa and Zimbabwe [9]. Acute myeloid leukemia (AML) is diagnosed with equal frequency as ALL in children in tropical Africa, and is especially common in boys aged 5 to 14 years, who present often with chloromas, usually arising in the orbit[10]. From the few reports of leukemias in Zambians it may be concluded that age and gender distributions of leukemias in Zambia resemble those of other sub-Saharan tropical African countries[11]. According to the latest WHO data published in 2018, leukemia deaths in Zambia reached 142 or 0.13% of the total deaths. The age adjusted death rate is 1.69 per 100 000 of population, ranking Zambia number 162 in the world [11].

Acute Myeloid Leukemia is more frequently seen in older adults. The incidence in the US is 3.5 cases per 100 000, being higher in patients over the age of 65 years compared with younger patients (15.9 vs 1.7, respectively), and causes approximately 2.1% of all cancer deaths in the US, with an annual death rate of 3.2 per 100 000 in 2007 [12].

The first attempt at classifying Acute Leukemia was the French American British (FAB) morphological criteria that divided ALL into 3 subtypes (L1, L2 and L3) and AML (into Mo-M7) based on cell size, cytoplasm, nucleoli, vacuolation and basophilia [13]. In 1997, the World Health Organization proposed a composite classification in attempt to account for morphology and cytogenetic profile of the leukemic blasts.

Etiologically, it has been studied in the pediatric population and later affirmed that genetic syndromes do predispose to a minority of cases of ALL, such as Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia and Nijmegen breakdown syndrome. Other predisposing factors include exposure to ionizing radiation, pesticides, certain solvents or viruses such as Epstein - Barr virus and Human Immunodeficiency Virus, which could not be confirmed in our patient. Furthermore, in the majority of cases, it appears as a de novo malignancy in previously healthy individuals.

Most of the clinical manifestations of ALL reflect the accumulation of malignant, poorly differentiated lymphoid cells within the bone marrow, peripheral blood, and, extramedullary sites. Presentation can be nonspecific, with a combination of constitutional symptoms and signs of bone marrow failure such as anemia, thrombocytopenia, and leukopenia. Our patient presented markedly with bleeding diathesis, associated symptoms of anemia over seven days and 'B symptoms' (fever, weight loss, night sweats), easy bleeding or bruising, fatigue, dyspnea and infection. Involvement of extramedullary sites commonly occurs and can cause lymphadenopathy, splenomegaly or hepatomegaly in 20% of patients but were not elicited on physical exam. CNS involvement was not apparent in this patient supporting the current tenets that at the time of diagnosis, it may occur only in 5–8% of patients and present most commonly as cranial nerve deficits or meningism. X ray was normal and examination did not reveal mediastinal mass despite the predilection of some form ALL (T-cell ALL) to present with a mediastinal mass [14]. According to literature physical examination usually reveals lymphadenopathy in 33% of patients with leukemia, splenomegaly in 50%, and skin infiltration in 10%. Hepatosplenomegaly, tender joints or limbs, gingival hypertrophy, petechiae, and ecchymoses may also be noted [15].

Diagnosis is established by the presence of 20% or more lymphoblasts in the bone marrow or peripheral blood. Evaluation for morphology, flow cytometry, Immunophenotyping and cytogenetic testing is valuable both for confirming the diagnosis and risk stratification. Lumbar puncture with CSF analysis is standard of care at the time of diagnosis to evaluate for CNS involvement. If the CNS is involved, brain MRI should be performed. Other evaluation includes complete blood count with differential and smear to evaluate the other hematopoietic cell lines, coagulation profiles and serum chemistries. Baseline uric acid, calcium, phosphate and lactate dehydrogenase should be recorded to monitor for tumor lysis syndrome.

Accurate assessment of prognosis is central to the management of ALL. Risk stratification allows the physician to determine the most appropriate initial treatment regimen as well as when to consider allogeneic stem cell transplantation (Allo-SCT). Historically, age and white blood cell count at the time of diagnosis have been used to risk stratify patients. Increasing age portends a worsening prognosis. Patients over the age of 60 have particularly poor outcomes, with only 10–15% long-term survival.

In addition to the aforementioned prognosticators, it has long been recognized that response to initial therapy predicts outcome. Historically, treatment response was evaluated morphologically. Recently, it has become standard practice to evaluate patients for minimal residual disease (MRD) using molecular techniques such as flow cytometry and PCR. Several studies have shown the importance of MRD in assigning risk [16]

The National Comprehensive Cancer Network (NCCN) has developed recommendations to approach risk stratification. The National Cancer Institute defines adolescent and young adults (AYA) to be those aged 15–39 years. The NCCN recognizes that AYA may benefit from treatment with pediatric-inspired regimens and thus are considered separately from adults >40 years. The main treatment for acute lymphocytic leukemia (ALL) in adults is typically long-term chemotherapy. The treatment typically takes place in 3 phases namely; induction, consolidation and maintenance. The goal of induction chemo is to get the leukemia into remission. Drugs used may include vincristine, dexamethasone or prednisone and an anthracycline drug such as doxorubicin [17].

After induction therapy, patients receive three cycles of intensification therapy of methotrexate with leucovorin rescue and L-asparaginase. Eligible patients with high-risk disease and a matched donor, then can undergo allogeneic stem cell transplantation (Allo-SCT).

After induction, eligible patients may go on to Allo-SCT while all others go on to intensification/consolidation and maintenance. Consolidation varies in the different protocols, but generally utilize similar agents to induction and includes intrathecal chemotherapy and cranial radiation for CNS prophylaxis at times. Maintenance therapy consists of daily 6-MP, weekly methotrexate, and vincristine and a 5-day prednisone pulse every 3 months. Maintenance is administered for 2–3 years after induction, beyond which it has not been shown to have benefit [18]

The current treatment of patients with acute myeloid leukemia yields poor results, with expected cure rates in the order of 30–40% depending on the biological characteristics of the leukemic clone. Therefore, new agents and schemas are intensively studied in order to improve patients' outcomes.

Conclusion

Late presentation, delayed diagnosis and therapy is likely to negatively impact clinical outcomes in patients presenting with leukemia more so in resource limited settings. Much as there may be a record of success in the management of leukemia among pediatrics in contrast with adults, there is need to equip our health facilities and personnel with appropriate resources towards early clinical detection, diagnosis and treatment which measures are essential for successful management and favorable clinical outcomes.

Patient consent

Informed consent was obtained from the patient and caregiver

Conflict of Interest: The authors declare that there was no conflict of interest regarding the publication of the manuscript

Author contributions: All authors contributed towards the concept, design, reviews and ultimate write up of the manuscript

References

1. Plasschert SL, K. W. V. E., 2004. Prognosis in childhood and adult acute lymphoblastic leukemia: a question of maturation?. *cancer treat Rev,* 30(1), pp. 37-51.
2. Eguiguren JM, S. M. C. W. K. K. R. G., 1992. Complication and outcome in childhood acute lymphoblastic leukemia with hyperleukocytosis. *Blood,* Volume 46, pp. 871-875.
3. WHO, 2018. Acute lymphoblastic leukemia.
4. William CK, F. L. L. L. S. I. L. A. a. G. M., 2014. Childhood leukemia and lymphoma: African experience supports the role for environmental factors in leukaemogenesis. *Ecancermedicalscience,* Volume 8, p. 478.
5. Hunger SP, L. X. D. M. e. a., 2012. . Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group.. *J Clin Oncol. ,* 30(14), p. 1663–1669.
6. Thomas X, B. J. H. F. e. a., 2004. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial.. *J Clin Oncol.,* 22(20), p. 4075–4086.
7. Nachman JB, L. M. H. S. e. a., 2009. Young adults with acute lymphoblastic leukemia have an excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment: a report from the children's oncology group. *J Clin Oncol. ,* 27(31).
8. Larson RA, D. R. B. C. S. R. S. P., 1995. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and leukemia group B study 8811. *Blood,* Volume 85, pp. 2025-2037.
9. Paul B, M. J. M. A. L. L. N. F., 1992. A threeyear prospective study of 137 cases of acute leukaemia in Zimbabwe.. *Cent Afr J Med,* Volume 38: , p. 95–99.
10. Fleming AF, 1993. Leukaemias in Africa.. *7 (Suppl.):,* p. 138–141.
11. WHO, 2018. Acute lymphoblastic leukemia.
12. Luis V, J. B., 2011. Acute Myeloid Leukemia: Optimal Management and Recent Developments.
13. Bennett JM, C. D. D. M. F. G. G. D. G. H. e. a. .. & ., :., 1976. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol ,* Volume 33, p. 451–458.
14. Luis V, J. B., 2011. Acute Myeloid Leukemia: Optimal Management and Recent Developments.
15. Keith S, A. K. .., 2004. Acute Leukemia: Diagnosis, Management, and Potential for Cure.
16. Dongen JJMv, v. V. V. B. M. O. A., 2015. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. *Blood,* Volume 125, p. 3996–4009.
17. American Cancer Society, 2021. Typical Treatment of Acute Lymphocytic Leukemia. https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/treating/typical-treatment.html
18. Jabbour EJ, F. S. K. H., 2005. Adult acute lymphoblastic leukemia.. *Mayo Clin Proc,* Volume 80, p. 1517–1