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Acute Promyelocytic Leukaemia In Rwanda: A Case Series

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Abstract:

Introduction: *Acute promyelocytic leukemia (APML, APL) is a subtype of acute myeloid leukemia (AML), a cancer of the white blood cells. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. APL is characterized by the fusion gene transcript PML-RARA which is a translocation of chromosomes 15 and 17. Both hypergranular and microgranular APL are habitually related with disseminated intravascular coagulation (DIC) and expanded fibrinolysis. Coagulopathy is related with noteworthy early passing rates in APL patients.*

Objective*: the aim of the present study was to investigate the clinicopathological features and outcomes of seven cases of acute promyelocytic leukemias received at King Faisal Hospital, Rwanda between 2020 and 2023, and to provide a reference for the current detection and clinical treatment of acute promyelocytic leukemias in Rwanda.*

Methods*: A total of 60 consecutive acute leukemia cases (including 35 AML cases and 15 ALL cases), which were received at the Department of Hematology of King Faisal Hospital (Kigali, Rwanda) between January 2020 and December 2023, were reviewed. The WHO criteria published in 2016 were followed to diagnosis, and a peripheral blood smear/bone marrow aspirates and bone marrow biopsies were evaluated by qualified professionals.*

Cytogenetic and molecular analysis performed on peripheral blood and aspirates samples were collected from all the patients suspected with APL at the time of provisional diagnosis. Cytogenetic analysis was conducted using conventional G banding technology and fluorescence in situ hybridization and PML-RARA was detected using PCR.

Clinical data pertaining to the patients were obtained from their medical records. Baseline clinical and molecular characteristics, the time between diagnosis and outcomes and the intensity of therapy of the seven patients with acute promyelocytic leukemias were recorded.

Results : *A total of seven patients with APL were identified, including four males and three females. The median age at diagnosis of APL was 38 years (range, 19 50 years). Among the seven cases with APL, 3 were in high risk category, with a delayed diagnosis and passed away before the treatment is initiated. One patient presented Acute respiratory distress syndrome (ARDS) and was referred abroad for a better management and he is in remission up to now. The two remaining patients were treated with ATRA and ATO and completed all the cycles and are in remission up to now.*

Conclusion*: Previously considered one of the most fatal subtypes of AML due to the bleeding diathesis seen in patients, APL has now become the most curable form of AML, findings from the above cases showed that early detection, and prompt initiation of treatment of cases of acute promyelocytic leukaemias in Rwanda resulted in good outcome.*

I. Introduction

Acute promyelocytic leukemia (APML, APL) is a subtype of acute myeloid leukemia (AML), a cancer of the white blood cells. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. APL is characterized by the fusion gene transcript *PML-RARA* which is a translocation of chromosomes 15 and 17. In this subtype of acute myeloid leukemia anomalous promyelocytes prevail. Both hypergranular (or ordinary) APL and microgranular (hypogranular) sorts exist {1}. It accounts for 5-8% of AML cases in younger patients, with a lower relative frequency in elderly patients {2}. The disease can occur at any age, but most patients are middle-aged adults. The annual incidence rate is 0.08 cases per 100 000 population {3}

Both hypergranular and microgranular APL are habitually related with disseminated intravascular coagulation (DIC) and expanded fibrinolysis {4}. Coagulopathy is related with noteworthy early passing rates in APL patients {5}.

Because it was the first tumor that was successfully treated with a molecularly targeted drug, APL is an important model for cancer treatment and this represented a shift in the way cancer is treated {6}. The treatment of acute promyelocytic leukemia has undergone a significant transformation since the advent of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) {7}. With the utilization of regimens containing ATRA in addition to arsenic trioxide, long-term overall survival rates of at least 95% are achievable in both low/intermediate and high risk APL {8,9}.

Although in the right circumstances, APL is a curable disease and potential cure is an opportunity that should be available to all afflicted individuals, in the absence of timely diagnosis and treatment, outcomes remain poor. More than 60 years after its initial description, early death still remains the major problem in APL management {10}.

Patients with APL may be stratified into the following 3 risk categories on the basis of white blood cell (WBC) count and platelet count :Low risk - WBC count < 10,000/µL and platelet count > 40,000/µL, Intermediate risk - WBC count < 10,000/µL and platelet count < 40,000/µL and High risk - WBC count > 10,000/µL {11} . Reported studies from large cooperative trials have shown that more rational delivery of treatment and improved outcomes may derive from the use of risk-adapted protocols. In particular, patients at higher risk of relapse (ie, those presenting with WBC > 10 × 109/L) seem to benefit from treatments that include cytarabine in the ATRA-plus-chemotherapy scheme, whereas patients with standard-risk disease can be successfully managed with less-intensive regimens that contain ATRA and anthracycline-based chemotherapy {12} .

Treatment of APL is divided into three phases, each with its own objectives and these are Induction therapy which starts immediately after diagnosis with the goals to kill as many APL cells as possible, bring blood cell counts to normal levels, and decrease APL-related symptoms. This is known as a complete hematologic response (CHR), Consolidation therapy follow induction therapy. Its main goal is to convert the CHR into a remission, and finally Maintenance therapy aims to ensure that remission is maintained over time {13}.

As the current early detection and treatment of AML thus remains challenging in low income countries including Rwanda, the aim of the present study was to investigate the clinicopathological features and outcomes of seven cases of acute promyelocytic leukemias received at King Faisal Hospital, Rwanda between 2020 and 2023, and to provide a reference for the current detection and clinical treatment of acute promyelocytic leukemias in Rwanda.

II. Materials And Methods

A total of 60 consecutive acute leukemia cases (including 35 AML cases and 15 ALL cases), which were received at the Department of Hematology of King Faisal Hospital (Kigali, Rwanda) between January 2020 and December 2023, were reviewed. The WHO criteria published in 2016 were followed to diagnosis, and a peripheral blood smear/bone marrow aspirates and bone marrow biopsies were evaluated by qualified professionals.

Cytogenetic and molecular analysis performed on peripheral blood and aspirates were collected from all the patients suspected with APL at the time of provisional diagnosis. Cytogenetic analysis was conducted using conventional G banding technology and fluorescence in situ hybridization and *PML-RARA* was detected using PCR.

Clinical data pertaining to the patients were obtained from their medical records. Baseline clinical and molecular characteristics, the time between diagnosis and outcomes and the intensity of therapy of the nine patients with acute promyelocytic leukemias were recorded. Response criteria of acute promyelocytic leukaemia therapy, including complete remission (CR), CR with incomplete hematologic recovery, morphological leukemia free state and partial remission (PR), were defined according to the 2017 European LeukemiaNet criteria.

Ethical consideration: The study obtained an approval notice from King Faisal Hospital institutional board review (IRB).

III. Results

Patient characteristics. A total of nine patients with APL were identified, including three males and six females. The median age at diagnosis of APL was 38 years (range, 19 50 years).

Treatment and outcome of acute promyelocytic leukemias by cases:

CASE 1: A 29 years old male with fatigue, fever and ecchymosis. The patient has been diagnosed treated for the last 2 months for typhoid fever in a private cabinet and then a district hospital before being referred to our referral hospital.

The patient was received and immediately admitted in internal medicine department. The full blood count performed showed the following results: WBC (2.9x10^3/uL), RBC (1.12x10^6/uL), Hb (3.9g/dl), MCV (102fL), MCH (35Pg), Absolute neutrophils (0.25x10^3/uL), Absolute lymphocytes (1.88x10^3/uL) Absolute monocytes (0.75x10^3/uL and Platelets (14x10^3/uL).

The peripheral blood smear showed Leucopoenia with severe neutropenia. On scanning, an infiltrate of blasts was noted: It was a heterogeneous population of medium to large sized cells with an abundant and moderately basophilic cytoplasm, clumped chromatin with irregular and convoluted or folded nuclear configuration and prominent nucleoli in some cells (image 1). Features on the peripheral blood smear suggested an acute leukaemia, most likely acute myeloid leukaemia, and flow cytometry for immunophenotyping of the cells and cytogenetics were recommended to refine or revise the diagnosis as needed.

Immunophenotypic analysis performed on this blood specimen has revealed 60-65% intermediate quite complex myeloid blasts. In particular, they were highly suggestive of and would best fit a diagnosis of Acute Promyelocytic Leukaemia and the assessment of the PML-RARA/t(15;17) was performed.

KARYOTYPING showed 46,XY,t(15;17)(q24;q21). Abnormal male chromosome complements with a translocation between the long arms of chromosome 15 and chromosome 17. The segments distal to these breakpoints have been exchanged which has resulted in the PML-RARA fusion. The presence of this chromosome abnormality confirmed the diagnosis of Acute Promyelocytic Leukaemia.

Follow up and outcome: At that time there was no treatment for acute myeloid leukemia in the country. The patient developed a pneumonia and was admitted in ICU for pneumonia and died few days later from this pneumonia before a treatment is initiated.

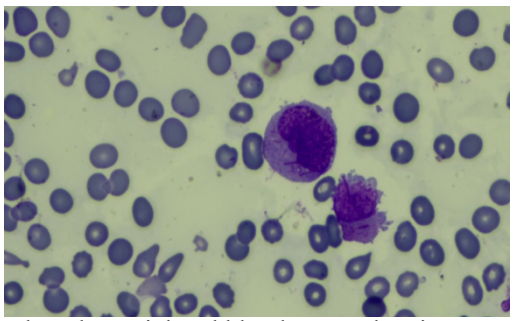


Image 1: Immature cells observed on the peripheral blood smear showing population of medium to large sized cell with an abundant and moderately basophilic cytoplasm and Auer rods.

Case 2: A 19 years old female with ecchymosis; otherwise healthy looking was received at the OPD on 10-08-2020. The full blood count performed showed the following results: WBC (50.32x10^3/uL), RBC (2.12x10^6/uL), Hb (6.7g/dl), MCV (89.2fL), MCH (31.6Pg), Absolute neutrophils (17.01x10^3/uL), Absolute lymphocytes (5.27x10^3/uL) Absolute monocytes (27.22x10^3/uL and Platelets (31x10^3/uL). The coagulation studies showed decreased fibrinogen levels and increased D-dimer.

The peripheral blood smear examination showed an infiltrate of blasts representing around 90% of all WBC and they are medium to large sized with mostly abundant granular cytoplasm. In some blasts granules obscured the nuclear margins. Nuclei were bilobed and Auer rods clearly visible. These features were suggestive of acute myeloid leukaemia (AML) favoring acute promyelocytic leukaemia subtype (image 2).

Immunophenotyping with flow cytometry revealed 90% complex immature myeloid cells. and KARYOTYPING revealed a reciprocal translocation between the long arms of one chromosome 15 and one chromosome 17 with breakage and reunion occurring at bands 15q24 and 17q21. These features were in keeping with the diagnosis of acute promyelocytic leukaemia.

Follow up and outcome: At that time there was no treatment for acute myeloid leukemia in the country. The patient died few days later following a massive intracranial hemorrhage.

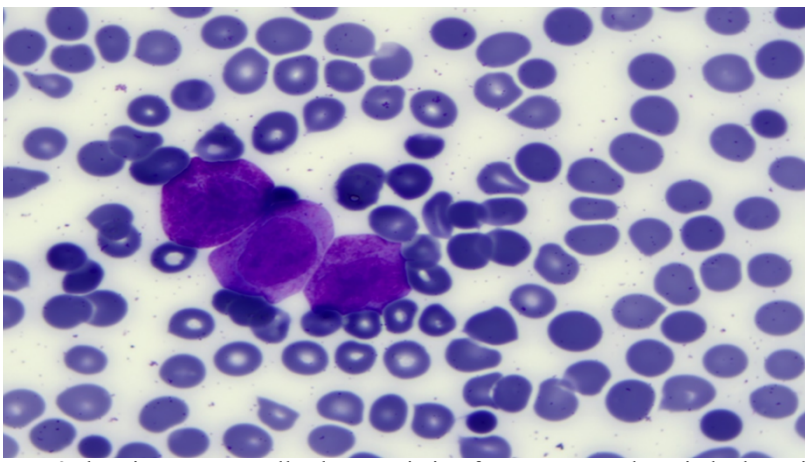


Image 2 showing Faggot cells characteristic of acute promyelocytic leukaemia.

Case 3: A 42 years old female with history of dizziness, fatigue and ecchymosis since July 2020 referred for investigation of pancytopenia. She has been transfused with red cells and platelets.

The full blood count performed showed the following results: WBC (1.66x10^3/uL), RBC (2.47x10^6/uL), Hb (7.9g/dl), MCV (93.4fL), MCH (32.0Pg), Absolute neutrophils (0.09x10^3/uL), Absolute lymphocytes (1.22x10^3/uL) Absolute monocytes (0.33x10^3/uL and Platelets (25x10^3/uL).

Patient had a bone marrow aspirate collected on 28/9/2020: The particles were absent however the marrow is cellular. The majority of the cells seen was a population of moderate to large primitive cells, hypergranular cytoplasm, folded nuclei(cottage loaf shape) and inconspicuous nucleoli. Auer rods were noted with occasional faggot cells present and this was highly suggestive of an Acute myeloid leukaemia, best fitting an Acute Promyelocytic Leukaemia (image 3).

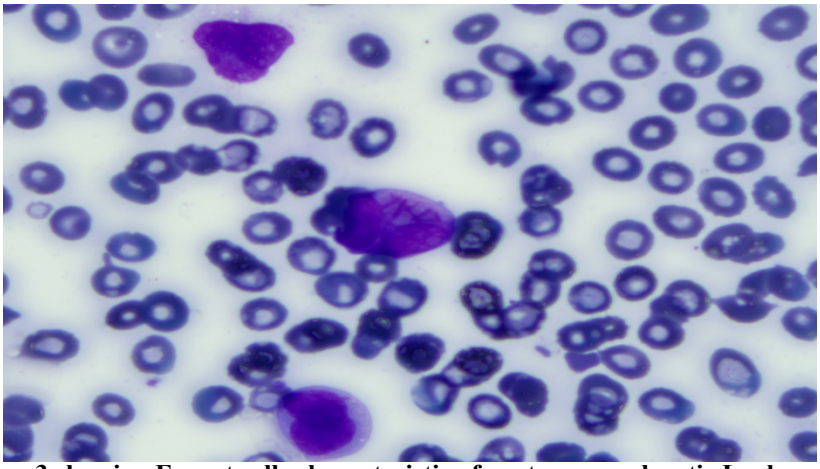


Image 3 showing Faggot cells characteristic of acute promyelocytic Leukaemia.

Immunophenotyping 72 % immature myeloid cells with maturation arrest in the granulocytes, best fitting the diagnosis of acute promyelocytic leukaemia and Fluorescence in situ hybridisation (FISH) analysis with the Metasystems XL PML/RARA Dual Colour, Dual Fusion. Translocation Probe Kit performed on bone marrow showed evidence of a *PML/RARA* gene rearrangement in 114 of 136 (84%) interphase nuclei scored. This confirmed the diagnosis of acute promyelocytic leukaemia.

Patient management and outcome:

The patient received transfusion with Platelets, cryoprecipitate, FFPs and RBCs. She was then treated with ATRA and ATO from 26th October 2020 to 19th June 2021 with Induction phase of 28 days ATRA taken every day and ATO from Monday to Friday. Consolidation phase with 4 cycles (1 cycle = 2 months); ATO: 4 weeks on and 4 weeks off (Monday to Friday) and ATRA : 2 weeks on and 2 weeks off.

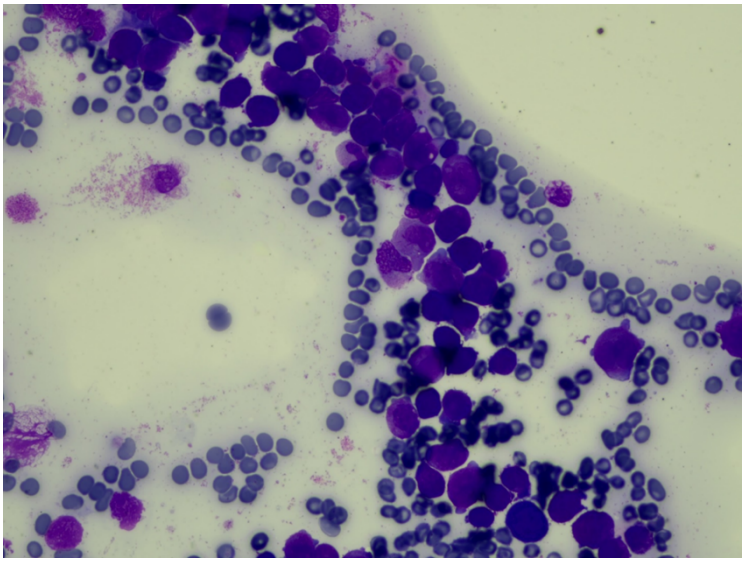
FBC, BMA&B and PML-RARA were analyzed after 1st cycle and 4th cycle. The table below shows the FBC results before and after treatment.

FBC parameters	Before treatment	After treatment
WBC	1.66	5.93
RBC	2.47	4.58
Hb	7.9	12.2
MCV	93.4	84.9
MCH	32.0	26.6
PLT	25	388
ABSOLUTE NEUTROPHILS	0.09	3.05
ABSOLUTE LYMPHOCYTES	1.22	2.39
ABSOLUTE MONOCYTES	0.33	0.40

The bone marrow aspiration and biopsy showed remission features and translocation probe kit performed on peripheral blood on 29th January 2021 showed no evidence of a *PML/RARA* gene rearrangement in 130 interphase nuclei scored. Patient is still in remission up to now.

Case 4: A 44 years old female with history of dizziness, fatigue and pancytopenia since November 2021. The FBC performed on 15th December 2021 showed the following results: WBC (1.13x10^3/uL), RBC (2.43x10^6/uL), Hb (7.8g/dl), MCV (92.6fL), MCH (32.1Pg), Absolute neutrophils (0.18x10^3/uL), Absolute lymphocytes (0.62x10^3/uL) Absolute monocytes (0.31x10^3/uL and Platelets (13x10^3/uL).

The Bone marrow slides from referring hospital showed a population of >20% blasts, these were medium in size, high N:c ratio, hypergranular cytoplasm, the granules often masking the nuclei. Primitive nucleus, most of them are folded (cottage loaf), inconspicuous nucleoli, easily seen Auer rods and faggot cells were also noted (image 4).



Bone marrow slides from referring hospital showed a population of >20% blasts, these are medium in size, high N:c ratio, hypergranular cytoplasm, the granules often mask the nuclei. Primitive nucleus, most of them are folded (cottage loaf), inconspicuous nucleoli. Auer rods are easily seen, faggot cells are also present.

PCR for *PML/RARA* on a bone marrow sample was recommended for definitive diagnosis and this confirmed the diagnosis of acute promyelocytic leukaemia.

Patient management and outcome:

The patient received transfusion with Platelets, cryoprecipitate, FFPs and RBCs. She was then treated with ATRA and ATO from 29/12/2021 up to 19/08/2022 with Induction phase of 28 days ATRA taken every day and ATO from Monday to Friday. Consolidation phase with 4 cycles (1 cycle = 2 months); ATO: 4 weeks on and 4 weeks off (Monday to Friday) and ATRA: 2 weeks on and 2 weeks off.

FBC, BMA&B and PML-RARA were analyzed after 1st cycle and 4th cycle. The table below shows the FBC results before and after treatment.

FBC parameters	Before treatment	After treatment
WBC	1.13	3.23
RBC	2.43	3.34
Hb	7.8	10.1
MCV	92.6	93.6
MCH	32.1	30.4
PLT	13	213
ABSOLUTE NEUTROPHILS	0.18	2.13
ABSOLUTE LYMPHOCYTES	0.62	0.94
ABSOLUTE MONOCYTES	0.31	0.13

Outcome: FISH for PML-Rara, done on 5th September 2022 was negative. Up to now she is still in remission.

Case 5: A 50 years old male patient with leukocytosis otherwise healthy looking. The FBC performed on 8th August 2022 showed the following results: WBC (94.23x10^3/uL), RBC (3.14x10^6/uL), Hb (9.1g/dl), MCV (88.2fL), MCH (29.0Pg), Absolute neutrophils (21.16x10^3/uL), Absolute lymphocytes (16.62x10^3/uL) Absolute monocytes (53.87x10^3/uL and Platelets (46x10^3/uL).

The peripheral blood smear examination demonstrated abnormal promyelocytes, large in size with abundant grey cytoplasm, cottage loaf, primitive nuclei and prominent nucleoli. Auer rods were present and some were faggots cells (image 5). These features were suggestive of Acute Promyelocytic Leukaemia (APL). Flow cytometry was recommended as well as FISH for t(15;17) for definitive diagnosis. Meanwhile, a treatment was initiated for this patient but he passed away 2 days after starting induction therapy.

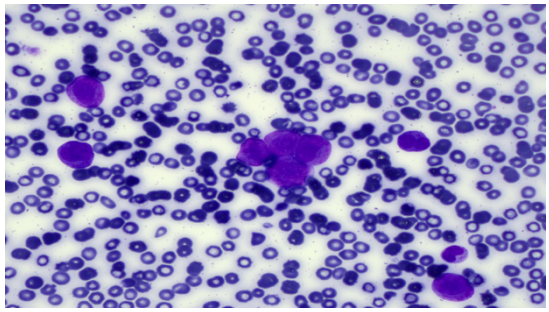


Image 5 showing Faggot cells characteristic of acute promyelocytic Leukaemia.

Case 6: A 34 years old male patient admitted in internal medicine department for spontaneous nosebleeds and bruises. The full blood count results showed WCC: 181 x10^3/uL,Hb: 7.1 g/dl MCV: 102.6 fL, Platelets: 32 x10^3/uL. A peripheral blood smear performed revealed an increased number of Blasts. These represented 90% of all WBC and were medium in size, with high N:C ratio, granular scanty cytoplasm, bilobed primitive nuclei, inconspicuous nucleoli (image 6). Some blasts were having bundles Auer rods (Faggot cells). These features were highly suggestive of acute promyelocytic leukemia. Unfortunately, the patient died shortly after this provisional diagnosis.

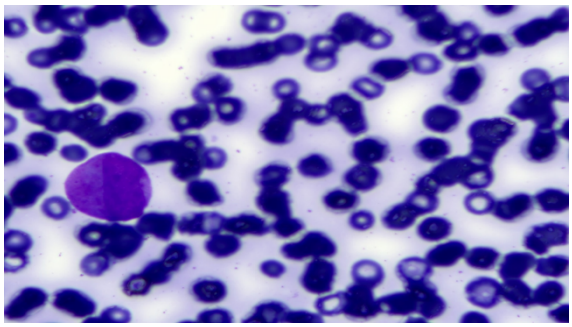


Image 6 showing Faggot cells characteristic of acute promyelocytic Leukaemia.

Case 7: A 38 years old male patient received on 22nd July 2023 in emergency and accident department and admitted in high dependent unit (HDU) with fever, respiratory distress and bleeding tendencies.

The FBC performed showed the following results: WBC (50.5x10^3/uL), RBC (1.66x10^6/uL), Hb (6g/dl), MCV (111fL), MCH (36.6Pg), Absolute neutrophils (3.60x10^3/uL), Absolute lymphocytes (7.25x10^3/uL) Absolute monocytes (38.50x10^3/uL and Platelets (18x10^3/uL). The peripheral blood smear showed that blasts were representing around 90% of all WBC. These were medium to large in size, high N:C ratio, grey agranular cytoplasm although some have fine granulations. Primitive nuclei, some are bilobed; prominent nucleoli are present and Auer rods are present (image 7), however there are no faggots cells. Neutrophils and lymphocytes are markedly reduced.

An acute promyelocytic leukaemia was suspected for this case and FISH for t(15;17) for PML-RARA and flow cytometry were recommended. The patient was categorized in high risk APL and in this case the antimetabolite cytarabine should be added to induction regimens, but this chemotherapy was not available at the hospital. Meanwhile the patient developed a pneumonia with acute respiratory failure. The patient was evacuated abroad for better management and he is now in remission.

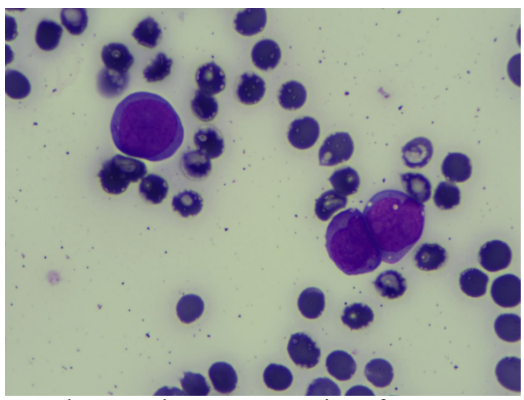


Image 6 showing abnormal promyelocytes suggestive of acute promyelocytic Leukaemia.

IV. Discussion And Conclusion:

Conventionally, AML patients are categorized into good, intermediate and poor-risk groups according to cytogenetic changes. AML classification based on these abnormalities is essential for accurate diagnosis, risk stratification, prognostic value, monitoring of minimal residual disease, and developing targeted therapies [14].

Current management of patients with AML is determined by a number of parameters, including age, performance status and the cytogenetic/molecular genetic characteristics of the leukemic clone. Together, these factors have an important bearing on treatment strategy and identification of potential candidates for molecularly targeted therapies [15].

Cytogenetic results allow the stratification of patients with AML into three classes, favorable, intermediate and unfavorable, according to clinical prognosis that is reported in the literature. So, patients with t(8;21)(q22;q22), inv(16)(p13q22) and t(15;17)(q24;q21) have a favorable prognosis with good response to treatment and complete remissions. On the other hand, patients with t(9;11)(p22;q23) are considered to have intermediate prognosis, and patients with t(6;9)(p23;q34), inv(3)(q21q26) and t(1;22)(p13;q13) present an unfavorable prognosis due to the aggressiveness of the disease and poor response to treatment. These cytogenetic alterations produce fusion genes that encode aberrant proteins with altered functional characteristics [1].

Currently, treatment for Acute Myeloid Leukemia (AML) is unavailable at Butaro Hospital and in other hospitals in Rwanda which may prompt to seek chemotherapy for AML outside of the country and this is associated with delayed patient management. The cost of such chemotherapy is generally quite high for patients in low income countries.

Previously considered one of the most fatal subtypes of AML due to the bleeding diathesis seen in patients, APL has now become the most curable form of AML {10, 11}, findings from the above cases showed that early detection, and prompt initiation of treatment of cases of acute promyelocytic leukaemias resulted in good outcome.

Even though, delayed diagnosis and management are the major causes of deaths and the outcome from the above case reports highlight the necessity of designing agreed and approved diagnostic and management protocols for this subtype of AML in Rwanda. The introduction of cytogenetic and molecular analysis would allow the identification of cases with good prognosis and in some cases such as APL, the management is easier and does not requires sophisticated logistics as the One-Step Detection Kits provide reagents to detect and quantify the fusion gene transcripts using total RNA isolated from blood or bone marrow in patients with acute leukaemias {16}.

The cost of diagnosis and management of APL seems to be high but when considered in the context of national priorities and solidarity; it is not expensive. Hence ATRA, ATO, Cytarabin and anthracyclines (Daunorubicin, Idarubicin) should be added in the list of essential drugs and cytogenetics and molecular analysis should be covered by the community health-based insurance (CBHI) scheme for poor families, and vulnerable groups.

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