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Unexpected diagnosis in not so usual clinical scenarios: Acute promyelocytic leukemia – A tertiary care hospital experience

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ABSTRACT

Background: Acute promyelocytic leukemia (APL) is a distinct subtype of Acute myeloid leukemia (AML) with arrest in maturation of cells of myeloid series in bone marrow. PML-RARA fusion resulting from t(15;17) translocation forms the genetic basis of this haematological malignancy. Introduction of specific differentiating targeted therapy i.e. All-trans retinoic acid (ATRA) have remarkably improved the outcome of this previously dreaded AML. **Aims and Objective:** The current study presents five cases of Acute promyelocytic leukemia with unusual presentations followed by effective treatment to revert their adverse outcome. **Materials and Methods:** In this retrospective evaluation of Acute Myeloid leukemia cases, five cases were included from duration of November 2019 to November 2021. The diagnosis of AMLs was made according to EGIL 1998/WHO 2016 guidelines. Peripheral blood (PB) and bone marrow aspirate (BMA) were stained with Giemsa and cytochemistry included myeloperoxidase (MPO) and periodic acid-schiff (PAS). **Results:** Five color flowcytometric analyses were performed on BMA and PB samples. Chemotherapy was administered in the patients and follow-up was done. 03/05 patients faced mortality due to rapid disease progression. **Conclusion:** The fast track clinical course from presentation to the outcome of APL is dreadful for the treating clinician and the heamatopathologist. Cytomorphology and Cytochemistry are as important in rapid recognition of APL as Immunophenotyping and Cytogenetics for establishing accurate diagnosis.

Key words: Acute Promyelocytic Leukemia, Diagnosis, Pathology, Follow-up, Coagulopathy

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INTRODUCTION

Leukemia since ages had been an unfortunate occurrence in human race, with its literal meaning being increased white blood cells in blood. Acute myelogenous leukemia (AML) is a type of malignant condition of bone marrow, which is due to maturation arrest of myeloid lineage progenitors which finally results in ineffective physiological hematopoiesis. Acute promyelocytic leukemia (APL) is a subtype of AML.

In reappraisal of the WHO classification of myeloid neoplasms and acute leukemia 2016, significance of the PML – retinoic acid receptor α (RARA) fusion was reinforced; hence, APL was renamed as APL with PML-RARA fusion, that is, APL with PML-RARA fusion. PML-RARA fusion results from t (15; 17) translocation in APL, which results in the fusion of the RARA gene on chromosome 17 and the PML gene on chromosome 15.[1] This entity has been exactly reinstated in the WHO classification of AML, 2022. Pharmaceutical knowledge of this cytogenetic pathology has leaded us to a breakthrough therapy in APL, that is, all-transretinoic acid (ATRA). ATRA, which is an analog of vitamin A, enables the maturation-arrested cells in bone marrow to overcome the inhibition of RARA, leading to expedition of myelogenous cells to neutrophilic stage maturation. Neutrophils have a life span of 6 h on an average,

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all the tumor cells which have matured to neutrophils, decline rapidly. This leads to brisk clearance of tumor cells from body. The effect is very specific; AMLs without translocations involving RARA do not respond to ATRA.[2] Arsenic trioxide (ATO) is given to treat the patient of APL as an adjunct to ATRA due to its effects in inducing apoptosis, downregulating BCL-2, and altering cellular redox reaction.[3]

With such promising pharmaceutical aid reserved for APL, it becomes obligatory for the physician and the pathologist to reach the diagnosis promptly and treat in most prudent manner. APL commonly has dramatic presentation of severe coagulopathy; hence, it becomes a race against time for the medical fraternity to pull the patient back from edge of demise.

Concerning the same, the present study presents riveting cases of APL with unusual presentations followed by prompt diagnosis with high possibility of APL and effective treatment to revert their adverse outcome.

Aims and objectives

The current study presents five cases of Acute promyelocytic leukemia with unusual presentations followed by effective treatment to revert their adverse outcome.

MATERIALS AND METHODS

In this retrospective evaluation of acute myeloid leukemia cases, five cases were included from duration of November 2019–2021, which took the clinicians and the hematopathologists by surprise. Clinical details of the patient were collected from the requisition forms archived in department of pathology for hematological investigations including peripheral blood (PB) examination, bone marrow examination, and flowcytometric analysis. The diagnosis of AMLs was made according to EGIL 1998/WHO 2016 guidelines.

All the specimens for hematological work-up were acquired with standard techniques. Three milliliters of blood samples were received in ethylenediaminetetraacetic acid vials for complete hemogram including PB smears. The blood samples were run within 4 h of collection in automated hematology analyzers (Sysmex XT 2000i and XN 1000i). Total leukocyte count (TLC), differential count, hemoglobin, platelet count, and red blood cell parameters were evaluated. PB and bone marrow aspirate (BMA) were stained with Giemsa stain and cytochemistry consisting of myeloperoxidase (MPO) and periodic acid-schiff using standard manufacturer specified staining instructions.

Five color flowcytometric analyses were performed using Beckman and Coulter FC500 flow cytometer on BMA and PB samples. Standard lyse-wash procedure was used followed by incubation at the room temperature for 15 min. Permeabilization of cells was done for the cytoplasmic markers. Various combinations of fluorochrome labeled monoclonal antibodies such as fluorescein isothiocyanate, phycoerythrin, electron-coupled dye, phycoerythricyanin 5 (PC5), and phycoerythricyanin 7 (PC7) were utilized to stain the cells of interest. Gating of blasts was done using CD45 versus side scatter. The following markers were used in the panel: CD45, CD19, CD20, CD10, CD79a, CD22, CD123, CD38, CD56, HLADR, CD34, CD117, TDT, CD1a, CD2, cCD3, CD7, CD4, CD8, CD14, CD16, CD11c, CD64, CD13, CD33, and cMPO.

CASE REPORTS

Following is the five cases included in the study, from their presentations to their respective outcomes (Table 1).

Case 1

A 13-year-old female presented to gynecological outpatient department (OPD) with chief complaints of heavy menstrual bleeding since menarche, increasing in episodes and days per months. Pallor was evident on patient, with her hemoglobin of 3.6 g%. By convention, the gynecologist work-up of the patient for bleeding diathesis, polycystic ovarian syndrome, endocrinopathies, Mullerian anomalies, and polyps (after excluding possibility of pregnancy). Her complete blood count revealed severe pancytopenia. The patient was transfused with two packed cell volumes during her 1st day in course of her hospital stay. PB smear of the young female patient displayed heavily granulated myeloid cells with rare presence of a mature neutrophil and bilineage cytopenia with differential count of 11 promyelocytes, five polymorphs, 81 lymphocytes, and three monocytes. Flowcytometric analyses could not be performed due to COVID pandemic; however, bone marrow examination was advised, which revealed near total replacement of bone marrow with monomorphic population of myeloid progenitor cells with coarse granulation, twisted, and folded nuclei. Erythroid series was markedly suppressed and showed normoblastic reaction. Overall the features were suggestive of acute leukemia infilteration of the bone marrow. Tumor cells were positive for CD15 IHC, while negative for PAX 5 and TdT.

Case 2

A 22-year-old pregnant female from rural area, with poor cohesion to antenatal clinic check-ups, presented to labor room of obstetric casualty in labor pains. Protocol during COVID-19 pandemic mandated testing for the same; hence, the patient was found to be COVID-19 positive on rapid diagnostic testing. On physical examination, the patient had pallor. Call for requisition for packed red blood cells blood transfusion was sent, along with complete

Table 1: Salient features of case reports of acute promyelocytic leukemia

Clinical and hematological characteristics	1	2	3	4	5
Age/Sex	13/F	22/F	14/M	25/M	19/F
Clinical presentation	Heavy menstrual bleeding at menarche	Postpartum hemorrhage	Continued bleeding from trauma to foot	Hemoptysis	Gluteal region abscess
Hb (g%)	3.6	5.8	4.5	6.9	5.7
TLC (/mm^3)	5150	57,690	8,070	26,000	6220
Plt (/mm^3)	15,000	17,000	11,000	23,000	6,000
Peripheral smear	Bicytopenia with 11% promyelocytes	Leukocytosis with 96% promyelocytes	Bicytopenia with 56% promyelocytes	Bicytopenia and leucocytosis with 71% promyelocytes	Bicytopenia with 83% promyelocytes
Bone marrow examination	Total replacement of bone marrow with monomorphic population of myeloid progenitor cells with coarse granulation, twisted and folded nuclei	Not done due to increased bleeding tendency	Not done due to increased bleeding tendency	Not done due to increased bleeding tendency and untimely demise	Not done due to increased bleeding tendency and untimely demise
FCM positive expressions	Not done in view of COVID pandemic	Not done in view of COVID pandemic	CD13, CD33 cMPO with CD14, CD64	CD13, CD33 cMPO with CD14, CD64 and CD58	CD13, CD33, cMPO with CD14, CD64, CD58 and CD38
Treatment	ATRA based Induction+ATO based consolidation	NA	ATRA based Induction	NA	NA
Outcome	Alive after 18 months of follow-up	Expired	Responded well to Induction therapy, following which patient lost to follow-up	Expired	Expired

blood counts investigation. CBC revealed severe anemia with Hb of 5.8 g% with leukocytosis (TLC=57,690/mm^3) and thrombocytopenia (Platelet count= 17,000/mm^3). Her parturition progressed and after vaginal delivery, she manifested as postpartum hemorrhage (PPH). The patient was transfused with packed cell volumes and was managed for PPH. Despite active management, patient's condition deteriorated and was shifted to obstetric and gynecological CCU. D-dimers, IL-6, and PT/INR were sent to exclude COVID-related coagulopathies. Peripheral smear examination revealed differential leukocyte count of 96 atypical promyelocyte, three myelocytes, and one meta-myelocyte. The atypical promyelocytes were 2–3 times the size of small lymphocytes, with scant to moderate amount of eosinophilic agranular cytoplasm, with irregular nuclear contours with nuclear grooving, clefting and bi-lobation, fine chromatin, and inconspicuous nucleoli. Few Auer rods also identified in few cells. Overall features were suggestive of APL with Bicytopenia. Flowcytometry was not put up as the patient was COVID-19 positive. Further, bone marrow examination was advised. However, due to unfortunate demise of patient, further, work-up could not be continued.

Case 3

A teenage 14-year-old male presented to Medicine OPD with chief complaints of continued bleeding from trauma left foot since 3 days. Application of pressure was ineffective at home. At presentation, the teenager was also found to be having high-grade fever with chills and rigor. There was history of few episodes of vomiting, which was followed by bleeding from mouth which increased with coughing. On further asking, attendants also revealed about passing of black-colored stools in 2 weeks. The teenager also complained about diminution of vision of the left eye. There was no significant family history. There was no history of easy bruisability/bleeding episodes/hematuria. The patient was immediately worked up for platelet function disorders. In CBC, his platelets counts markedly reduced (11,000/mm^3). He had severe anemia (Hb=4.5 g%) with TLC within normal limits (8070/mm^3). However, DLC had 56 promyelocytes, 17 blasts, two polymorphs, and 29 lymphocytes. Here, the atypical promyelocytes also showed apple-core appearance of nucleus and polarization of granules. Very occasionally faggot cells were also seen. On flowcytometry, features were suggestive of APL with coexpression of CD14 and CD64, with HLA-DR negative and CD117 negative expression. The patient responded well to induction therapy of 60 days. Definite outcome could not be known as patient was lost to follow-up.

Case 4

A 25-year-old male, native of rural India, presented to medical OPD with chief complaints of high grade fever and productive cough. Chest roentgenogram reveals

heterogeneous opacities in bilateral lung fields. The patient was immediately admitted in ward of Internal Medicine. Considering high prevalence of tuberculosis (TB) in India, work-up for TB was also done. The patient also developed hemoptysis during his hospital stay. His follow-up chest radiogram was suggestive of abscess right lung. His fever still kept intermittently rising and alleviating. Complete blood count from emergency laboratory revealed Hb of 6.9 g%, platelet count of 23,000/mm^3, and TLC of 26,000 with DLC of-atypical cell 71, polymorphs 11, lymphocyte 14, monocyte 2, and eosinophil 2 which were suggestive of Bicytopenia with leukocytosis? Chronic myeloid Leukemia? Leukemoid reaction. As blood loss was constant due to abscess right lung, the patient was transfused with PCVs. Initial 4 PCVs did not produced the expected rise in hematocrit and hemoglobin. CBC with peripheral smear examination was send for provisional causes of refractoriness of Bicytopenia to reference laboratory. Peripheral smear finding in this laboratory revealed presence of 14% blasts with marked myelodyspoietic cells. Mature myeloid forms showed hypolobation with hypergranulation and poor segmentation. These blasts cell were 2–2.5 times the size of small lymphocyte with moderate to abundant cytoplasm and vesicular chromatin. Few blast cells imparted nuclear cupping, nuclear grooving along with occasional polarization of granules and nuclear blebbing. Flowcytometry was also acquired and the patient was inferred as acute myeloid leukemia; promyelocytic variant with possibility of monocytic differentiation, that is, coexpression of CD14 and CD64. Expression of CD34 was negative and HLA-DR was dim positive. The patient expired after a brief ICU hospital course due to respiratory failure and DIC with APL as secondary cause of death.

Case 5

A 19-year-old female present to OPD of internal medicine with chief complaints of gluteal region abscess in the right side since 2 weeks and fatigability since 6 months which progressively increased, leading to alteration in her day to day life. Interestingly, two complete blood counts were retrievable from the archive of the pathology department, which were sent with 24 h of interval in between. These two sequential hemograms showed no significant change in hemoglobin levels (5.7 g%), but TLCs showed considerable increase from 2,300/mm^3 to 6,220/mm^3 and platelet counts decreased from 60,000/mm^3 to 6,000/mm^3. Peripheral smear examination, along with the second complete blood counts, showed bicytopenia with 83% of atypical promyelocytes in DLC. These atypical cells were 2–3 times the size of mature small lymphocytes with amphophilic scant to abundant granular cytoplasm. Nuclear features included bi-nucleation, apple core appearance and reniform appearance. No faggot cells or auer rods were noted. The same blood sample was taken up for flowcytometry, as bone marrow aspiration could not be performed in view of severe thrombocytopenia and progressively debilitating condition of the patient. Flowcytometric analysis of the patient was reported as AML-M3, that is, acute promyelocytic leukemia. The gluteal abscess was whether a manifestation of granulocytic sarcoma or not could not be evaluated due to rapid plunge in patient's condition and untimely demise (Figure 1).

DISCUSSION

According to the studies which discuss the geographical variation in incidence of AMLs, Indian population has the fortune of being one of the lowest in rate of childhood AMLs.[4] The median age of presentation in current case series was 19 year of age, which is almost a decade younger than the reported median age of presentation of APL in Indian population.[5] Factually, the cases of APLs in this present study are either teenagers or young adults (13–25 years).

The clinical presentation of the APL usually has defined clinical course, morphological features and therapeutic management than other AMLs. Non-specific symptoms include fatigue with significant decrease in daily endurance of physical burden. APLs are notorious for their dramatic presentation with hemorrhagic manifestations. We had similar presentation in four out of five (80%) reported cases in form of menorrhagia since menarche, PPH, and prolonged continued bleeding after traumatic injury to

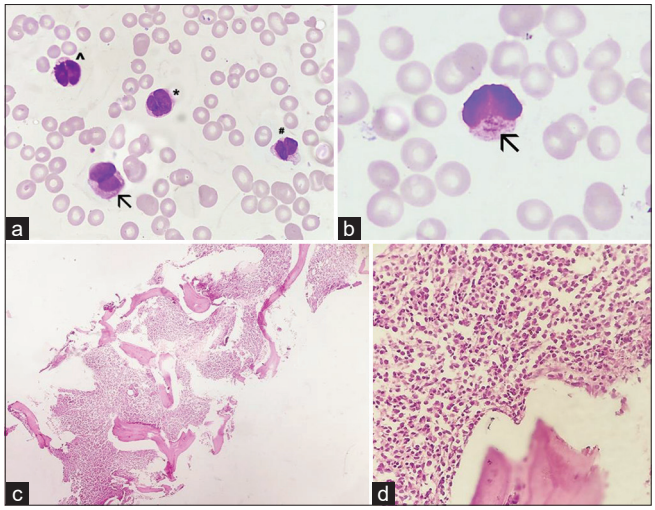

Figure 1: (a) Peripheral blood smear showing leukocytosis, with presence of atypical promyelocytes and absence of mature neutrophils (×600). # Promyelocyte showing nuclear folding and abundant granular cytoplasm, Arrow – promyelocyte showing apple-core nucleus, Asterix – promyelocyte showing trilobation, ^Promyelocyte showing bi-lobation. (b) Promyelocyte showing Auer rods (Oil-immersion, ×1000). (c) Bone marrow trephine biopsy showing hypercellular marrow (×40). (d) Bone marrow sections show replacement of normal hematopoietic cells with atypical promyelocytes (×100)

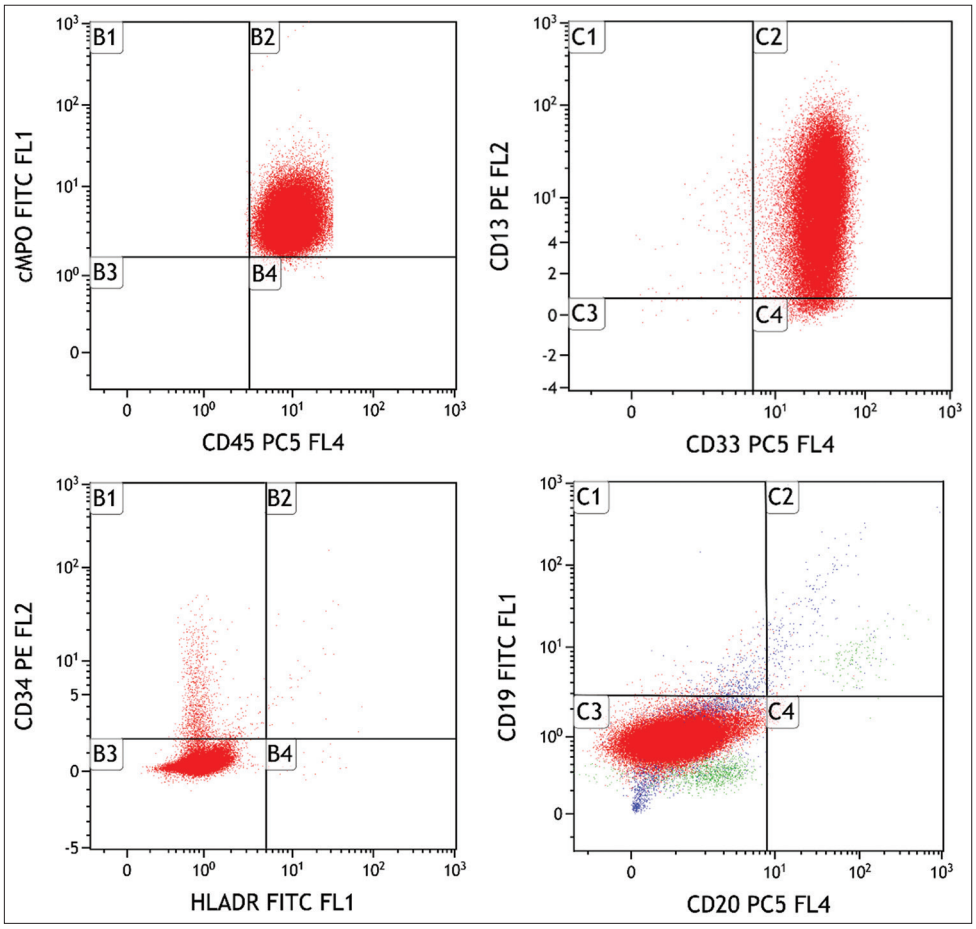

Figure 2: Dot plots of flowcytometry depicting – Positive expression of CD45, MPO, CD33, and heterogeneous CD13 expression. Dim to negative expression of HLA-DR and CD34. Negative expression of CD20 and CD19

foot. These hemorrhagic complications are generally out of proportion to the underlying degree of thrombocytopenia and rarely show any improvement on platelets and coagulation factors transfusion. Patients may also present with thrombotic complications such as deep venous thrombosis, pulmonary embolism, and cerebrovascular accident.[6] Some patients with advanced disease may present with overt disseminated intravascular coagulation. CNS bleeds are also not unheard in APL.[6] It was also clinically suspected in case 3, that diminution of vision in the patient was result of a CNS bleed.

While duration of diagnostic work-up of patients, the primary complete blood counts usually revealed pancytopenia. A prompt coagulopathy workup including a platelet count, prothrombin time (PT), activated partial thromboplastin time, D-dimer or fibrin split products, and fibrinogen has also been found of utility. On further work-up for determining the etiology of pancytopenia or the hemorrhagic manifestation of patients, PB smear examination shows presence of atypical promyelocytes which are usually heavily granulated and show various distinct nuclear features such as nuclear folding, bi-nucleation, hypolobation, apple-core appearance, dumb-bell shaped nucleus, nuclear cupping, and nuclear grooving.[7] Four out of five cases in our study gave a near confirmed diagnosis of APL on PB examination itself. Hypergranulation of atypical promyelocytes, auer rods, or foggot cells were identified in four out of five cases. Hypogranular variant is uncommon in AMLs and is present in one-third of acute promyelocytic leukemic cases.[8] It is vital to appreciate hypogranular variant as it has higher leucocyte count and shorter turnover time of atypical promyelocytes.[9]

Bone marrow examination was not done in four out of five cases (80%) included in our study due to increased bleeding tendency of the patients. Flowcytometric evaluation was used in three out of five cases (60%) to confirm the diagnosis (Refer Figure 2). These cases maintained their lineage loyalty showing strong positivity for cMPO, CD13, and CD33. Coexpression of CD33 and CD13 was also very evident in all three cases. During normal hematopoiesis, there is presence of CD13 before the acquisition of CD33. Two of the cases displayed antigenic positivity for CD14 and CD64, which were inferred as monocytic

differentiation. CD64 is also expressed by promyelocytes through metamyelocytes maturation normally.[10] HLA-DR remained dim positive to negative. Physiologically too, maturation of myeloid lineage is characterized by loss of CD34 and HLA-DR at the promyelocytic stage.[11] Case 4 also showed considerable antigenic expression of CD11c, which could be owed to the fact of comparatively high differential count of neutrophils in this case. Segmented neutrophils display higher expression of CD11b, CD11c, CD10, CD16, and CD15.[10] There was variable antigenic expression of CD117. CD58 was also strongly positive in all three cases, which is remarkable as CD58 is biologically a marker of cytotoxic T-cell proliferation. Here, cytotoxic T-cells are performing anti-leukemic role. Higher expression of antigen HLA-DR and CD58 is indicative of better chances of complete remission (CRm) in AMLs.[12]

Rapid deterioration in clinical condition from presentation to death was observed in three out of five of these cases, which is in concordance with the conventional course of APL. Historically, APL was an entity which was aggressively managed on low-dose heparin, blood products transfusion, and critical care management. Yet despite the dedicated supportive measures, mortality rates remained high in patients of APL in peri-induction period.[7] However, the sensational introduction of ATRA has made APL as one of the most curable form of AMLs. ATO has also been a reliable addition to ATRA in the therapeutic protocol of APL. It is mandated to start ATRA administration as soon as the diagnosis is suspected based on primary PB smear, and even before the confirmation of the diagnosis by genetics, cytogenetics, or immunostaining techniques.[13]

ATRA-based induction therapy, with ATO or anthracycline-based chemotherapy, is given until CRm is achieved or 60 days, whichever is earlier. An initial monitoring of response to induction therapy can be obtained through bone marrow aspiration and biopsy performed after approximately 30–35 days, usually when patients have absolute neutrophil count (>1000/ml) and platelet count (>100,000/ml) with independence from blood transfusions.[14] An earlier evaluation, such as that generally done for other variants of AML (for example, on day 14), is not recommended since it may be misleading.[14]

ATO (As_2O_3 or ATO)-based consolidation therapy for 6–8 months is usually recommended, with objective to achieve molecular CRm. However, in patient with leukocyte count >10,000/ml at presentation, anthracycline-based chemotherapy is recommended.[15] The evaluation of response to consolidation is done by BMA and biopsy samples, which are tested for the PML-RARA fusion transcript using reverse transcription-polymerase chain reaction (RT-PCR). Molecular CRm is defined by the absence of the PML-RARA fusion transcript using RT-PCR methods with a sensitivity threshold of at least 10^{-3} or 10^{-4} levels.[15]

Patients who have a positive RT-PCR at the conclusion of the planned consolidation phase should have a second BMA and biopsy for RT-PCR testing repeated after interval of 4 weeks. If the second test is negative, the patient may proceed to maintenance therapy. If the second RT-PCR is still positive, the patient should proceed to treatment for resistant disease.[15]

Maintenance therapy includes only monitoring if the patient had ATO- based consolidation. For the patients who had anthracycline-based consolidation, it is recommended to have ATRA intermittent dosing with or without 6-mercaptopurine and methotrexate for following 1 year after consolidation. Monitoring during maintenance includes RT-PCR on the PB or marrow every 3 months for the 1st year of CR, since patients have propensity to develop relapse in this duration.[15]

Limitations of the study

The case series included only five cases of APL with unusual presentation. Flowcytometric analysis could be performed in only three of of five cases presented in the case series. Cytogenetic studies were not performed due resource constraints.

CONCLUSION

In medical practice, the fast track clinical course from presentation to the outcome of APL is both exciting and dreadful for the treating clinician and the hematopathlogist. The aforementioned case scenarios have again reinforced the time sensitivity in diagnostic and therapeutic work-up of patients of APLs. In practicality, cytomorphology and cytochemistry are as important in rapid recognition of APL as immunophenotyping and cytogenetics for establishing accurate diagnosis.

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Authors' Contributions:
RG- Prepared first draft of manuscript, reviewed the literature and manuscript preparation; **SS-** Concept, Diagnostic management of the patients, interpreted the diagnosis and results; reviewed the literature and manuscript preparation; **LD, KB-** Preparation of manuscript and revision of the manuscript; **PKS, SG-** Clinical work-up of patients and management.

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