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CASE REPORT

Acute Promyelocytic Leukaemia With PML – RAR α Fusion Presenting as Pancytopenia and Atypical Morphology – A Case Report

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Abstract

Acute myeloid leukaemia (AML) is characterised by uncontrolled proliferation of malignant marrow stem cells and is associated with infection, anaemia and bleeding. An improved understanding of pathophysiology has led to revamping the diagnostic, prognostic and therapeutic landscape of AML. AML is classified based on the defined genetic abnormalities and based on the differentiation. AML with predominance of abnormal promyelocytes shows characteristic t(15;17)(q24.1;q21.2) leading to promyelocytic leukaemia – retinoic acid receptor alpha (PML – RARA) fusion oncoprotein. A 75-year-old male with features of acute promyelocytic leukaemia – hypogranular variant with atypical morphology and PML-RARA fusion is presented. The bilobed buttock shaped nuclei is an atypical presentation and is important to diagnose this morphology.

Key words: Leukaemia, promyelocytic, acute; Buttock cells; *In situ* hybridisation, fluorescence; Pancytopenia; Retinoic acid receptor alpha.

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Introduction

Acute myeloid leukaemia (AML) with promyelocytic leukaemia – retinoic acid receptor alpha (PML – RARA) fusion is classified under AML with defined genetic abnormalities in World Health Organization (WHO) 2022 classification. The other terminology is acute promyelocytic leukaemia (APL) with t(15;17)(q24.1;q21.2) / PML-RARA under AML with recurrent genetic abnormalities in 2022 International Consensus Classification (ICC). APL was formerly termed as AML M3 by the French-American-British Classification (FAB). APL is a type of acute leukaemia showing predominantly promyelocytes and PML-RARA fusion. It is common among young to middle aged adults. With current treatment regimens, cure rates are more than 90 %.[1]

Case history

A 75-year-old male was admitted in the Department of Medicine with complaints of breathing difficulty for 4 months, poor intake of food for 1 month, cold, cough and weight loss for 2 months. There was no history of fever, vomiting and loose stools. He was a known hypertensive patient on treatment. He was not a known case of leukaemia, pulmonary tuberculosis or diabetes. On examination, patient was conscious, oriented, dyspnoeic, afebrile and had bilateral pedal oedema. Basal crepitations were heard on auscultating the lung fields. Clinical diagnosis was systolic hypertension / chronic obstructive pulmonary disease/ chronic kidney disease.

His blood sample was received in the Depart-

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ment of Pathology laboratory for complete blood count and peripheral smear examination. The complete blood count results were as follows: white blood cells (WBC): 1900 cells/mm^3, red blood cells (RBC): 2.04 x 10^6 cells/mm^3, haemoglobin (Hb): 6.7 g/L, haematocrit (HCT): 19.5 %,

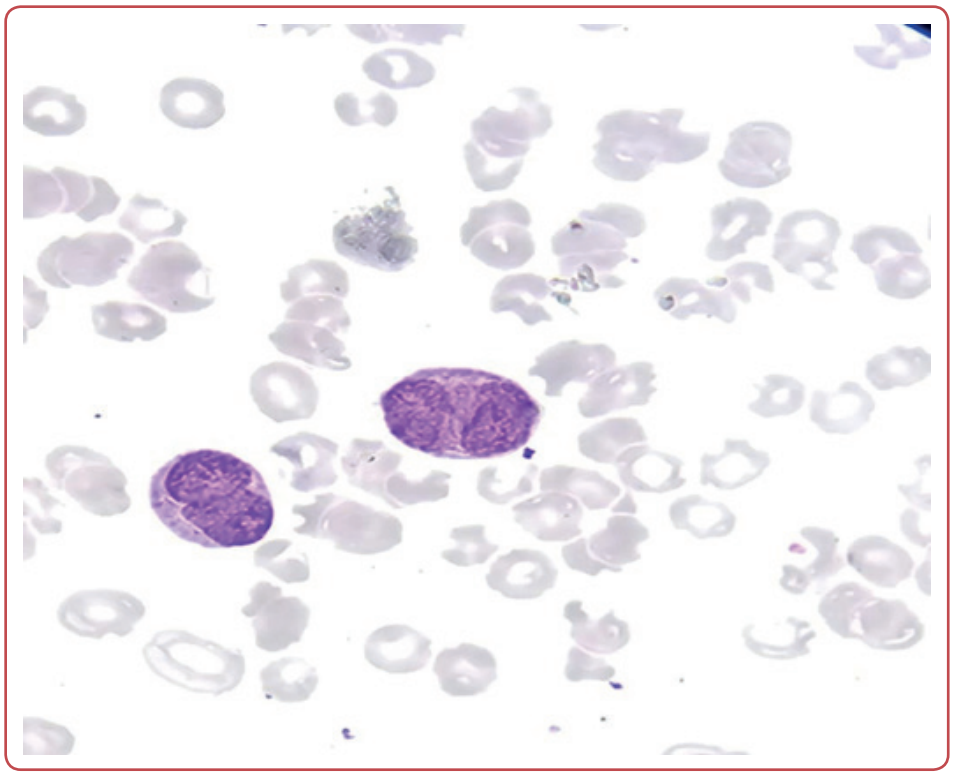

Figure 1: Buttock cells in acute promyelocytic leukaemia

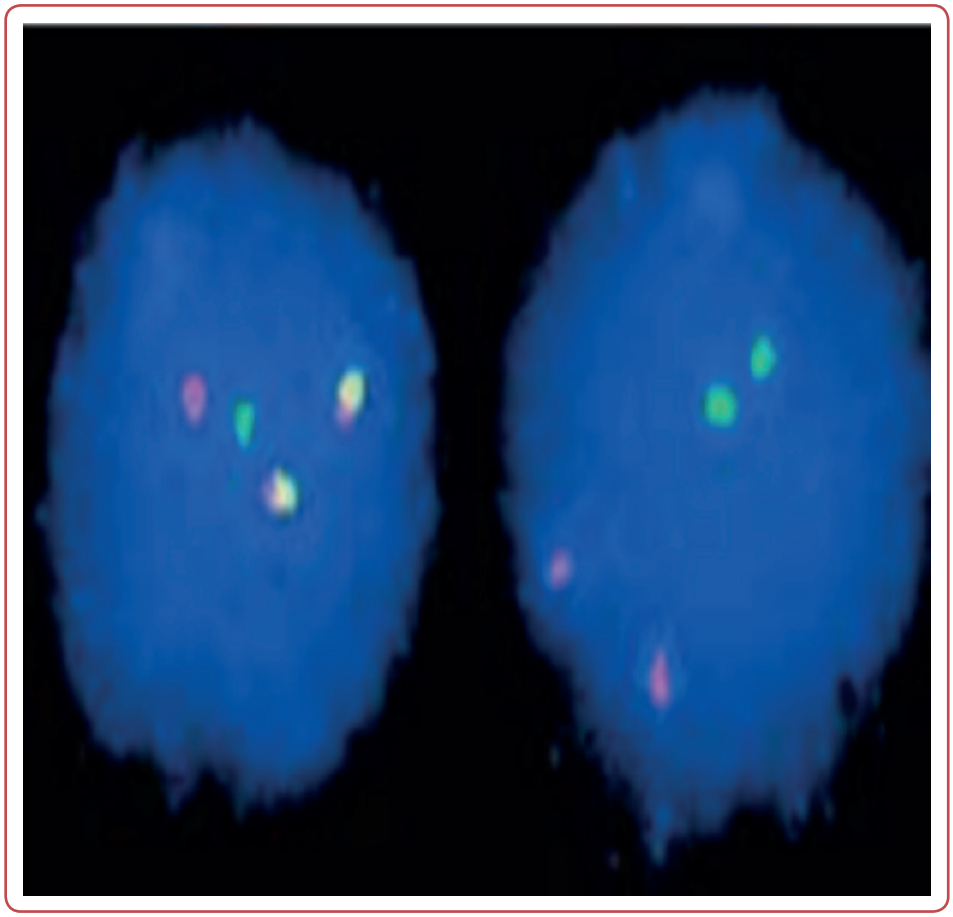

Figure 2 Fast fluorescent in situ hybridisation (FISH) showing promyelocytic leukaemia – retinoic acid receptor alpha (PML – RARA) fusion

mean corpuscular volume (MCV): 95.6 fL, mean corpuscular haemoglobin (MCH): 32.8 pg, mean cell haemoglobin concentration (MCHC): 34.4 g/dL, neutrophils: 46.2 %, lymphocytes: 21.6 %, monocytes: 31.2 %, eosinophils: 0.5 %, basophils: 0.5 %, platelets: 31000 cells/mm^3, red blood cell distribution width – standard deviation (RDW-SD): 75.2 fL, RDW-coefficient of variation (RDW-CV): 23.4 %, blasts / abnormal lymphocytes: 300 cells/mm^3, nucleated red blood cell (nRBC): 300. Peripheral smear was done and stained with Leishman's stain. Smear showed microcytic hypochromic red blood cells with 1-2 nRBCs /100 WBC were found. Total leucocyte count was reduced with 30 % of atypical buttock shaped blast cells. The cells were large with basophilic cytoplasm and buttock shaped cleaved nuclei having coarse chromatin. Platelets were reduced in count. A hypothesis of acute leukaemia probably acute PML- hypogranular variant was made (Figure 1). Bone marrow aspiration/ flow cytometry was suggested for confirmation.

Blood sample was collected in lithium heparin vacutainer for fluorescent *in situ* hybridisation (FISH). ZytoLight SPEC PML/RARA1 dual colour dual fusion probe was used. The result was abnormal with 80 % of the nuclei showing PML-RARA fusion t(15;17), thus confirming the diagnosis of APL (Figure 2).

Discussion

APL is a type of AML with defined genetic abnormalities. It is more common among young and middle-aged adults (20 to 59 years). Two morphologic variants are hypergranular and hypogranular APL. It accounts for 5 % - 8 % of AML cases in younger patients. Incidence is high among Latin American population.[2] There is no gender predilection. Peripheral blood and bone marrow are commonly involved. Extramedullary involvement is rare. Aetiology is unknown, prior exposure to chemotherapy or radiotherapy play a role in some cases.

It is characterised by balanced translocation t(15;17)(q24.1;q21.2) leading to PML-RARA fusion oncoprotein. PML-RARA oncoprotein suppresses gene expression by recruitment of a number of transcriptional repressors, which leads to block in differentiation and malignant transformation of myeloid cells. PML-RARA is detected in 90 – 95 % of cases. The most frequent additional cytogenetic changes are trisomy 8 and deletion 7q.[3] In 5 % APL cases, variant RARA translocations is detected involving RARA gene at 17q21.2 and different partners. One of the partner genes is ZBTB16 at 11q23. Cases involving ZBTB16 gene have a poor response to all trans retinoic acid and arsenic trioxide and a characteristic morphology. PML-RARA fusion is detected by FISH technology. Leucopoenia is a common presenting sign in traditional APL. Leucocytosis is common in the microgranular variant.[4] Patients may present with symptoms of pancytopenia are fatigue, weakness, infection, bleeding. There is a high risk of coagulopathy and disseminated intravascular coagulation (DIC), especially in microgranular acute promyelocytic leukaemia. DIC is the main cause of death in APL.[4] Release of thromboplastin-like substance from the granules of promyelocyte causes DIC. Patients with DIC have prolonged prothrombin time (PT) / activated partial thromboplastin clotting time (aPTT), D-dimer and fibrin and fibrinogen degradation product (FDP).

Peripheral blood smear in hypogranular variant shows leucocytosis with numerous abnormal promyelocytes bilobed or buttock / reniform / convoluted nuclei with sparse granules (dusty granules) or maybe agranular. Only rarely Auer rods / Phi bodies may be seen.[5] Presented case had atypical buttock shaped nuclei. The bilobed buttock shaped nuclei is an atypical presentation and is important to diagnose this morphology. Flow cytometry is an essential method that is widely used in the classification of AML and has an advantage giving the results within 2 h, thereby minimising the risk of death caused by the disease.[6]

All trans retinoic acid (ATRA) plus arsenic trioxide is currently the standard of care for low and intermediate risk APL patients.[7] In high-risk patients, chemotherapy is given along with all trans retinoic acid and arsenic trioxide.

Conclusion

The diagnostic and therapeutic importance of diagnosing this case with atypical morphology in peripheral smear is highlighted. Although DIC is a fatal complication in APL, it has a good prognosis when treated with ATRA and arsenic trioxide.

Ethics

Our institution does not require ethics approval for reporting individual cases or case series. A written informed consent for anonymised patient information to be published in this article was obtained.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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Writing - review and editing: SSK
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