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Case Report

Pathology Section

Acute Myeloid Leukaemia t(8;21)- A Close Differential Diagnosis to Myelodysplastic Syndrome with Excess Blasts-2: A Case Report

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ABSTRACT

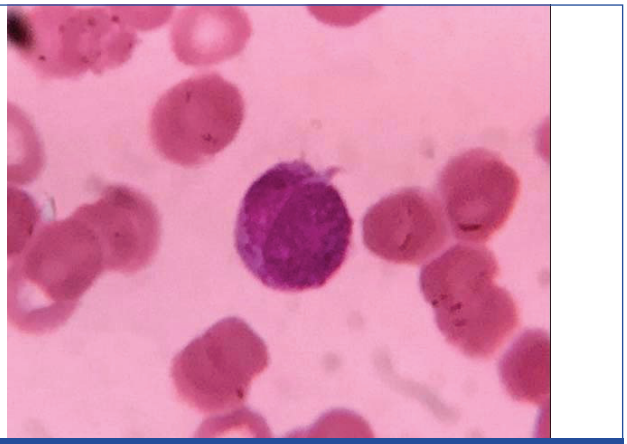
Acute Myeloid Leukaemia (AML) with t(8;21) (q22;22) is a distinct, rare type of AML, generally occurs in young patients which has a favorable prognosis. It is found in approximately 5% cases of all AML. This translocation (8;21) usually correlates with specific morphological features which include large blasts with auer rods and large Pseudo-Chediak-Higashi granules in neutrophils. These features are also seen in myelodysplasia related changes, hence should be differentiated as the latter have worse prognosis. Detection of chromosomal abnormalities by cytogenetics is very important for risk stratification and prognosis. Hence, authors reports a very unusual case of AML t(8;21) in a 32-year-old female patient presented with features of Myelodysplastic Syndrome (MDS) with Excess Blasts-2.

Keywords: Auer rods, Chediak-higashi granules, Chromosomal abnormalities, Cytopenia

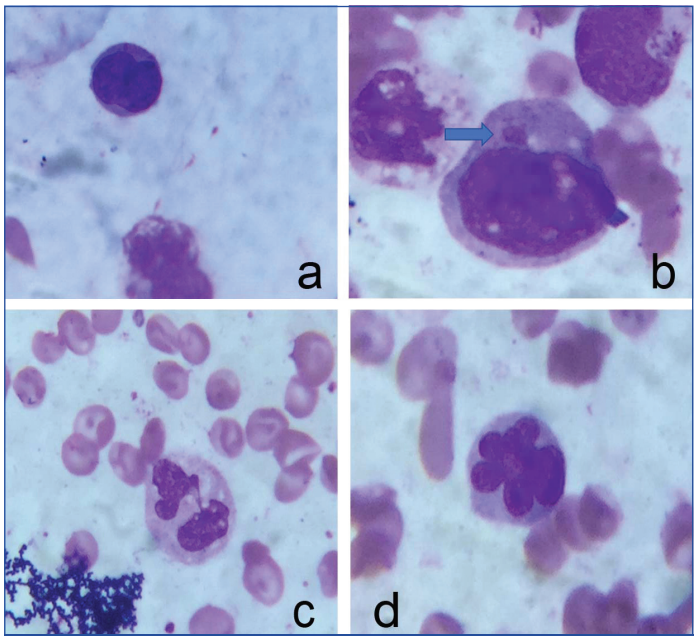
CASE REPORT

A 32-year-old female presented to the Emergency Department of Hospital with complaint of generalised weakness, fever and pain in abdomen for 25 days. She did not have any co-morbid illness in the past. Upon inspection, pallor was present on the face, nails and inner lining of eyelid. On palpation, she had mild hepatosplenomegaly. Other systemic examination did not show any significant findings or lymphadenopathy.

On laboratory investigation, full blood counts showed cytopenia with 3.4 g/dL haemoglobin, 10.5% haematocrit and 50×10^9/L platelet count. White Blood Cells (WBC) count was 7.3×10^9/L with 12% blasts. The blasts were large, basophilic cytoplasm and with multiple nucleoli. Auer rods were noted [Table/Fig-1]. Her coagulation parameters, liver function test and renal function test were within normal limits. Widal and dengue tests were negative. Bone marrow aspiration showed hypercellularity with few leukaemic blasts (upto 5%). The blasts were large, with abundant basophilic cytoplasm containing numerous large azurophilic granules (Pseudo-Chediak-Higashi granules) and auer rods [Table/Fig-2a]. Some blast show phi bodies [Table/Fig-2b]. Myelopoiesis was increased with dysplastic features [Table/Fig-2c]. Eosinophils and its precursors were also increased. Erythroid and megakaryocytic series were reduced in number and show dysplastic features [Table/Fig-2d]. Blasts showed Myeloperoxidase (MPO) staining positively. Bone marrow biopsy showed hypercellularity with features of multilineage dysplasia and presence of abnormal localisation of immature precursors [Table/Fig-3]. Hence a diagnosis of Myelodysplatic Syndrome (MDS) with Excess Blasts- 2 (MDS EB2) was given and cytogenetic analysis along with Flouroscent In-situ Hybridisation (FISH) was advised.



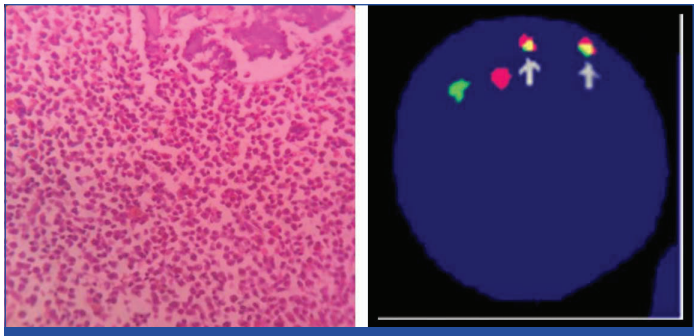
[Table/Fig-1]: Blast on peripheral smear (Leishman stain, X1000).



[Table/Fig-2]: Bone Marrow Aspiration showing- a) Blast (Geimsa stain, X1000); b) Blast with phi body (arrow) (Geimsa stain, X1000); c) Myeloid Dysplasia (Geimsa stain, X1000); d) Erythroid Dysplasia (Geimsa stain, X1000).

Cytogenetics: Subsequently markers for MDS panel deletion 5q, deletion 7q, deletion 20q came out to be negative. Conventional cytogenetic analysis also along with FISH showed fusion of gene i.e, *AML ETO* (translocation indicating positive for t(8;21) [Table/Fig-4].

This patient received two cycles of chemotherapy but unfortunately did not respond well to chemotherapy and succumbed after 2 months of diagnosis.



[Table/Fig-3]: Bone Marrow Biopsy (H&E stain, X400).
[Table/Fig-4]: Translocation indicating positive for t(8;21) (X1000). (Images from left to right)

DISCUSSION

Acute Myeloid Leukaemia (AML) was first identified by Rowley JD in 1973 [1]. The AML with balanced translocation are group of leukaemias characterised by recurrent genetic abnormalities of prognostic significance [2]. AML arising from MDS, denovo AML with multilineage dysplasia and AML t(8;21) has no significant differences morphologically but the former occurs in elderly and have worse prognosis [3]. Therefore detection of cytogenetic abnormalities and multilineage dysplasia are the most significant features of current AML classification [4].

Cytogenetic abnormalities are seen in 60% of newly diagnosed patients with AML and is used for determining prognosis. The t(8;21) abnormality is found in 5% to 10% cases of AML where in molecularly, the RUNX1 gene located at 21q22 fuses with RUNX1T1 on 8q22 forming RUNX1-RUNX1T1 fusion gene. These patients have favourable prognosis after intensive chemotherapy and low relapse rates. Other chromosomal abnormalities such as trisomy 4, trisomy 8, deletion 9q, their prognostic impact is not known [2,5].

World Health Organisation (WHO) criteria for AML is the presence of 20% or more blasts in the bone marrow. However according to WHO classification, if blasts <20%, but if associated with t(8;21) abnormality should be diagnosed and treated as AML [6]. The common morphological features in t(8;21) are presence of large leukaemic blasts with azurophilic granules and some with auer rods. The bone marrow shows granulocytic maturation to promyelocytes, myelocytes, mature neutrophils with or without dysplastic changes. These blasts are positive for markers like CD13, CD33, CD34, myeloperoxidase [7].

Patients with AML t(8;21) have a favourable prognosis after intensive chemotherapy and low relapse rate [5]. AML with multilineage dysplasia was first defined by Brito-Babapulle E et al., and later it was seen prevalent in 20% patients with AML [8]. The significance of prognosis is controversial but recent studies suggest that it does not affect the outcome of patient with AML [9].

AML with Myelodysplasia related changes is an acute leukaemia with 20% or more blast in peripheral blood or bone marrow with morphological features of myelodysplasia or associated with prior history of MDS or myeloproliferative disorder (MPN) or MDS/MPN genetic abnormalities. Patients should also not have specific genetic abnormalities of AML with recurrent genetic abnormalities and not have history of prior cytotoxic or radiation therapy. It mainly occurs in elderly patients and is rare in children [10].

In MDS, there are two categories: (Refractory Anaemia with Excess Blasts) RAEB-1 and RAEB-2.

- **RAEB1:** is a MDS with 5%-9% blasts in bone marrow and 2%-4% in peripheral blood.
- **RAEB-2:** is a Myelodysplastic Syndrome (MDS) with 10%-19% blasts in bone marrow and 5%-19% in peripheral blood. The presence of auer rods qualifies RAEB-2 irrespective of blast percentage. The peripheral blood for such patients generally show abnormalities in all the three myeloid cell lines. The bone marrow is hypercellular and degree of dysplasia may vary.

The erythroid precursors show dyserythropoesis including presence of abnormally lobulated nuclei and bridging. Granulopoesis is frequently increased and shows dysplasia in the form of nuclear hypolobation in neutrophils (pseudo pelger huet nuclei) or hypersegmentation, hypogranularity and/or Pseudo-Chediak-Hegashi granules. Megakaryopoesis is frequently normal or increased and tendency to form clusters.

In biopsy, blasts tend to form clusters and are located away from bony trabeculae and vascular structures- Abnormal Localisation of Immature Precursors (ALIP). Approximately 25% of cases of RAEB-1 and 33% of RAEB-2 progress to AML [11]. Hypocellular AML-M4 is an infrequent entity, almost have myeloid phenotype and usually develops secondary to radiation or chemotherapy. The diagnosis of hypocellular AML-M4 is a challenging for both physician and pathologist because of common features with hypocellular AML, hypocellular MDS, aplastic anaemia including cytopenia and dysplasia [12].

It is defined as hypocellular marrow with >20% blasts and none or few blasts in the circulating blood. It is unclear whether the leukaemia is secondary to the hypocellularity or if it is primary event. It has been suggested that leukaemia cell population inhibit myelopoesis through a humoral mechanism or increased susceptibility of myeloid precursors to the inhibitor in older patients might play a role in the genesis of hypoplasia [12].

In present case report, the female presented with all dysplastic features in erythroid and myeloid lineage in bone marrow with blast upto 5%. But blasts showed presence of auer rod, so it was diagnosed as MDS RAEB-2 on bone marrow examination. Further cytogenetic studies showed presence of t(8;21) translocation, therefore pointing towards AML.

CONCLUSION(S)

This case was challenging because morphological diagnosis of dysplasia can be unreliable as we see in other conditions like RAEB-2, AML with multilineage dysplasia, AML-M4. Hence, in all such cases, FISH and cytogenetic analysis is used to assess genetic abnormalities and in making early diagnosis. Limitation of this case report is the death of the patient inspite of good prognosis for AML t(8;21) were the limited value in accurate diagnosis on the basis of morphology demands the use of higher investigations like FISH, cytogenetics, immunophenotyping etc.

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