Diagnostic Challenging Case of Hypoplastic Acute Myeloid Leukemia with Literature Review

ABSTRACT:

Hypoplastic acute leukemia (HAL), also known as smoldering leukemia, is a form of atypical leukemia. It is a rare entity and currently defined as having cellularity of < 20 % in bone marrow with >20 % blasts at presentation. Hypocellular acute myeloid leukemia are more frequent than hypocellular variant of acute lymphoid leukemia. Although cases of hypoplastic acute myeloid in children and younger age group have been reported in literature, they are extremely rare. These cases pose a diagnostic challenge to the hematopathologist and treating physician, as hematological features of hypoplastic acute myeloid leuckemia (AML), hypocellular myelodysplastic syndrome and aplastic anemia are similar. Therefore, it is crucial to distinguish between these diseases as treatment modalities are different for each entity. Very few reported cases are available in literature. Hereby, we report this case of hypocellular AML-M0 in a 16-years-old Indian boy.

Keywords: Acute leukemia, bone marrow, hypocellular, hypoplastic leukemia, aplastic anemia

INTRODUCTION:

Usually acute leukemias present as hypercellular bone marrow[1], however infrequent presentation (< 10 % of all cases) with hypocellular bone marrow has been recognized[1,2]. Acute leukemias with bone marrow cellularity < 20 % are considered as hypoplastic acute leukemias, although in previous reports cellularity less than 40% was considered to be hypocellular[1,3,4]. It has been noted that acute myeloid leukemia presenting as hypoplastic acute leukemias is substantially more common than that of acute lymphoid leukemia[5,6]. The frequency of hypoplastic AML ranges between 5 % to 12 % of all cases of AML[5,7]. It usually occurs in adults and is frequently secondary to chemotherapy or radiation[5,8]. It is important to differentiate hypoplastic acute leukemias from aplastic anemia and hypoplastic myelodysplastic syndromes as these also exhibit peripheral cytopenia and bone marrow hypocellularity[1,5]. In order to help in differentiation between these disorders few guidelines have been proposed[9,10]. There is scarcity of reported cases in literature and very few reported cases with clinical outcome are available. Here we report a rare case of hypoplastic acute myeloid leukemia in anadolescent patient.

CASE PRESENTATION:

A 16-years-old boy presented to general medicine out patientdepartment with complaints of fever, which was mild grade and associated with chills and rigor, since last 1 month. He also has progressive dyspnea on exertion, generalized weakness and easy fatigability. On physical examination he had pallor. There was no lymphadenopathy or organomegaly.

Complete blood count revealed hemoglobin of 6.65 gm/dl, total leukocyte count of 1590/mm3, platelets of 158000/mm3 and atypical lymphocyte flagging. Peripheral blood

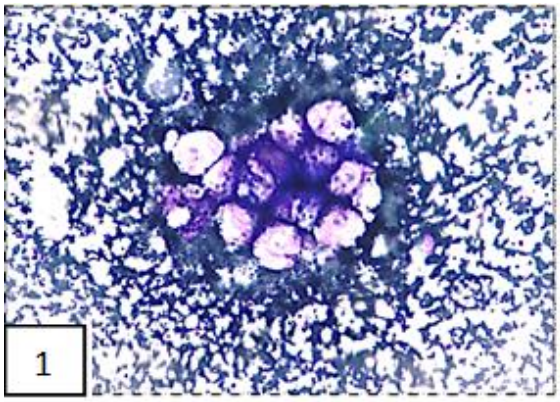
smear examination showed microcytic hypochromic blood picture with occasional tear drop cells, pencil cells and nucleated RBCs. The differential count was, neutrophils 2%, lymphocytes 96% and 2% atypical lymphocytes. Corrected reticulocyte count was 0.21%

Serum vitamin B-12 level were reduced. Serum iron level and percentage saturation were increased. Blood sugar, renal function test and liver function test were within normal limit and work-up for infections were negative.

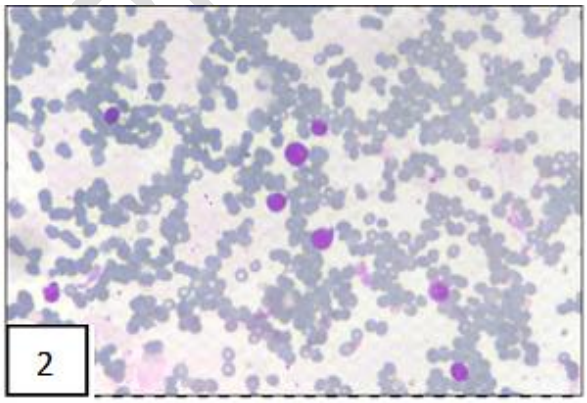
In view of decreased serum Vit. B-12 level and febrile neutropenia, he was started on Vit. B-12 supplementation and intravenous antibiotics but no improvement was noted clinically as well as hematologically.

In view of persisting pancytopenia with presence of atypical cells and no improvement in spite of treatment, bone marrow aspiration and biopsy were performed.

Bone marrow aspirate revealed hypocellular smears with presence of 38 % blasts (Fig. 1 and Fig. 2). These blasts had high nuclear cytoplasmic (N:C) ratio, open chromatin, prominent 1-2 nucleoli and scant amount of basophilic cytoplasm. Rest of the hematopoietic elements were relatively suppressed. A tentative diagnosis of 'Acute leukemia- Myeloid (hypoplastic)' was rendered.

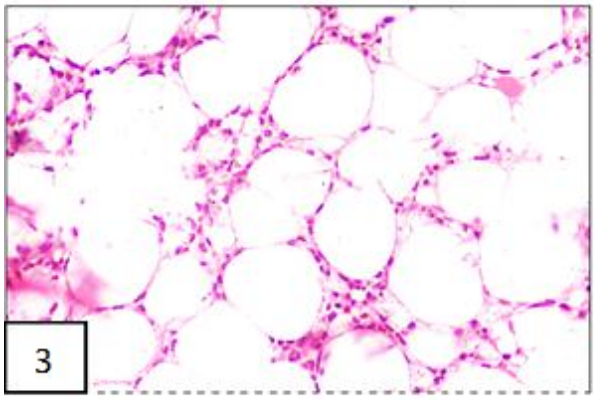


Bone marrow aspirate smear showing hypocellular marrow particle(400x, Leishman Giemsa stain)

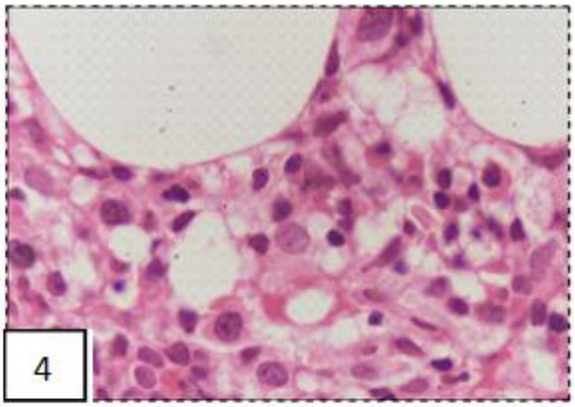


Bone marrow aspirate smear showing blasts cells (400x, Leishman Giemsa stain)

Bone morrow core biopsy was adequate and showed bony trabeculae enclosing hypocellular marrow with a cellularity being 20-25% (Fig. 3). Proliferation of blasts having high N:C ratio, vesicular chromatin, prominent 1-2 nucleoli and scant amount of cytoplasm were noted (Fig 4). Erythroid and myeloid series cells were relatively suppressed.

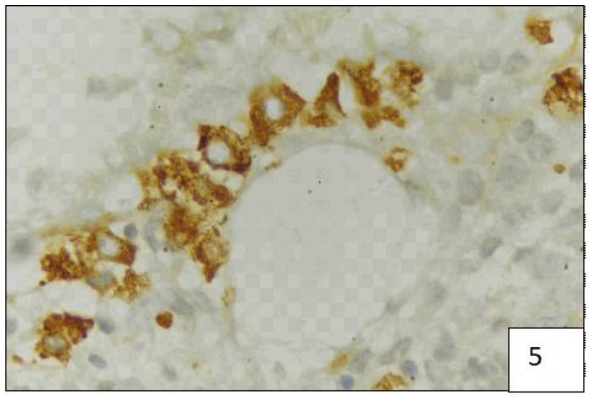


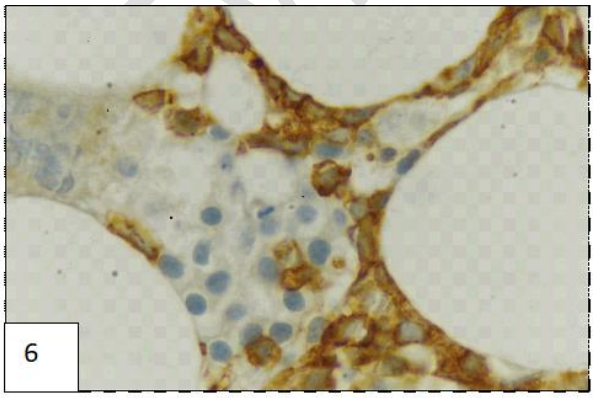
Bone marrow trephine biopsy showing hypocellular marrow for age (400x, H&E stain)



Bone marrow trephine biopsy showing blasts cells with prominent nucleoli (400x, H&E stain)

Immunohistochemistry showed myeloperoxidase (MPO) (Fig 5) positivity in blasts. There was strong membranous positivity for CD7(Fig 6) and CD34 (Fig 7). B cell and T cell markers (CD20, CD79a, CD3) and Tdt, CD117 were negative in the blasts.





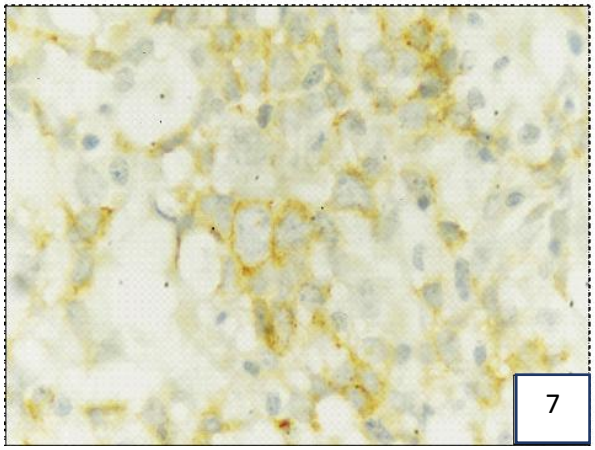


Fig. 5: MPO showing strong granular cytoplasmic positivity in blasts (1000x; IHC)

Fig. 6: CD 7 showing strong membranous positivity in blasts (1000x; IHC)

Fig. 7: CD 34 showing weak to moderate membranous positivity in blasts (1000x; IHC)

Final diagnosis of 'Hypoplastic acute myeloid leukemia AML-M0' was made.

DISCUSSION:

Hypoplastic acute leukemia (HAL) is well recognized though infrequent entity and is considered as an atypical leukemia[2,11].It defined as hypocellular marrow with > 20 % blasts and no or few blasts in circulating peripheral blood[11].There are a few case series and

individual case reports of HAL available inthepublishedenglishliterature.HAL is typically secondary in nature and it has been observed that they usually have a history of prior radiotherapy or chemotherapy or an antecedent hematological cancer[1,6].

Very few cases are reported from India. In the study done by Jain et al [2], two cases were included. One patient was of 13 years of age and had similar presentation as in our case. The approach to diagnosis and bone marrow findings are similar as in our study.There are only four case reports of hypoplastic AML in patients younger than 20 years of age from India available[1,2,11].Hypoplastic AML is defined as hypocellular marrow with 20% or more blasts in bone marrow which are MPO positive[5,11].It has been reported that these patients have a lower leukemic burden, undergo a more indolent course and, often respond well to remission induction therapy[1].

Pathogenesis of hypocellularity has not yet been established and it is debatable if the leukemia is a consequence of the hypocellularity or if it is the primary cause.Two potential mechanisms for hypocellularity have been proposed. First, it has been proposed that leukemic cells inhibit myelopoiesis through a humoral mechanism[12]. These inhibitory substances include leukemia inhibitor factor (LIF), stem cell inhibitor factor (SCI), tumor necrosis factor (TNF), prostaglandin E and decrease or aberrant stimulatory factor i.e., granulocyte colony stimulatory factor (G-CSF)[12]. Second, greater myeloid precursor susceptibility to the inhibitor may contribute to the development of hypoplasia in older individuals[13].

Nagai et al. first proposed a diagnostic criterion for HAL: (i) pancytopenia with rare appearance of blasts in peripheral blood; (ii) less than 40% bone marrow hypocellularity; (iii) more than 30% blasts in bone marrow of all nucleated cell; and (iv) myeloid phenotypes of leukemic blasts by myeloperoxidase staining and/or immunophenotyping[6].According to the WHO, diagnosis of acute leukemia requires more than 20% blasts.Our case fulfilled the above-mentioned criteria.

Phenotyping can be done using flowcytometry or immunohistochemistry.CD 34 is an important immunohistochemical markers for identifying the blasts[9]. CD117, MPO, and CD68 are helpful in subtyping[5]. In our case, phenotyping was done using immunohistochemistry on the bone marrow biopsy section. The blasts cells showed strong granular cytoplasmic positivity for MPO, weak to moderate membranous positivity for CD34 and strong positivity for CD7.

In a study Tuzuner et al. reviewed 14 patients with HAL, classified the cases according to FAB classification.Theyfound that M1 type predominated followed by M2 and M6[7].As per the FAB classification our case was classified as type M0.

Although we were unable to do genetic work-up in our patient, previous publications indicate that there is no difference between patients with hypoplastic AML with those who do not in terms of cytogenetic abnormalities[1]. Hypoplastic AML have lower frequency of RAS and FLT3 mutations[1].

The experience on treatment details is scarce however previous reports indicate that the disease has slow progression and frequently responds well to remission induction therapy[1,2]. Treatment modalities are similar for patients with or without hypocellular AML.

The beneficial effects of hematopoietic growth factorssuch as granulocyte macrophages colony stimulating factor (GM-CSF) have been reported in the treatment of hypoplastic AML following chemotherapy[14,15].It has been hypothesized that the leukemic cells might possess properties that make them sensitive to G-CSF. Leukemic cells proliferate slowly and are consequently characterized by a maturation failure. G-CSF effectively induces leukemic cell maturation and suppress the leukemic cell clone by inducing apoptosis.[14].

Despite the difficulties brought on by the rarity of hypoplastic AML, collaborativeefforts to gather and share data on this subtype are crucial for advancing research and enhancing patient care.

CONCLUSION:

Occurrence of hypoplastic AML is rare in young age and children.Larger study is the need of the hour to determine the precise prevalence of this condition. Even though its diagnosis is challenging for both hematopathologist and treating clinician, it should be diagnosed correctly to aid in a proper clinical management. Specific clinicalmanagementrecommendations are challenging because of the incomplete understanding of this entity's clinical and prognostic characteristics.

Consent

As per international standards, parental written consent has been collected and preserved by the author(s).

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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