



Diagnostic Challenging Case of Hypoplastic Acute Myeloid Leukemia with Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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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 leukemia (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.

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1. 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 an adolescent patient.

2. CASE PRESENTATION

A 16-years-old boy presented to general medicine out patient department 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.

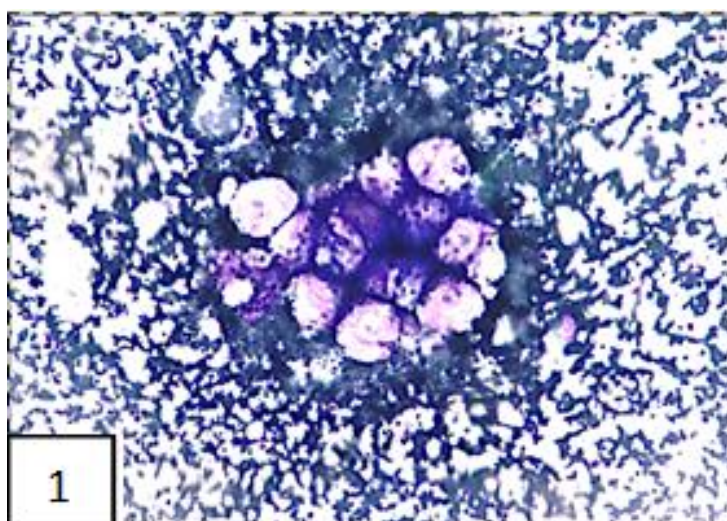


Fig. 1. Bone marrow aspirate smear showing hypocellular marrow particle (400x, Leishman Giemsa stain)

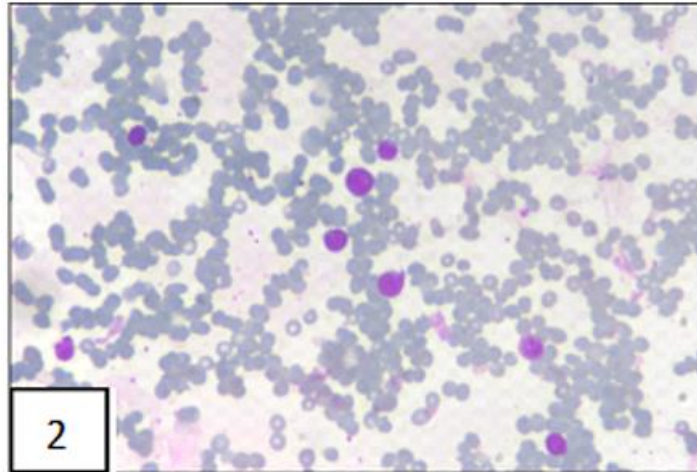


Fig. 2. Bone marrow aspirate smear showing blasts cells (400x, Leishman Giemsa stain)

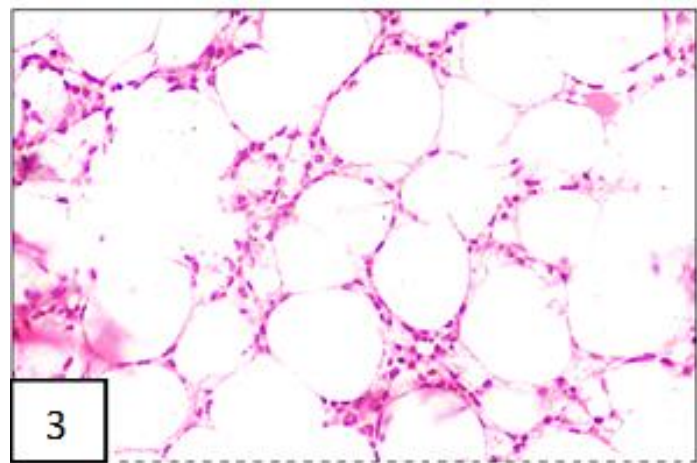


Fig. 3. Bone marrow trephine biopsy showing hypocellular marrow for age (400x, H&E stain)

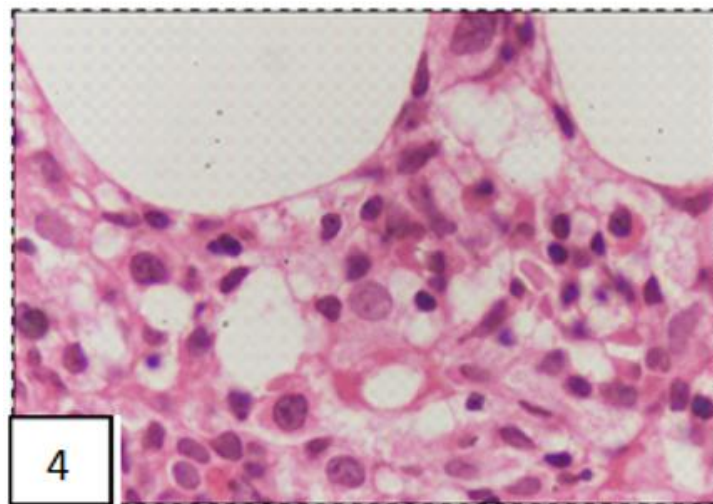


Fig. 4. Bone marrow trephine biopsy showing blasts cells with prominent nucleoli (400x, H&E stain)

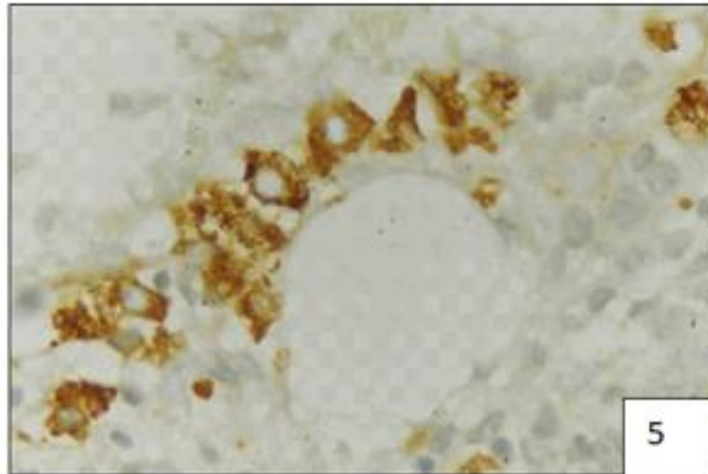


Fig. 5. MPO showing strong granular cytoplasmic positivity in blasts (1000x; IHC)

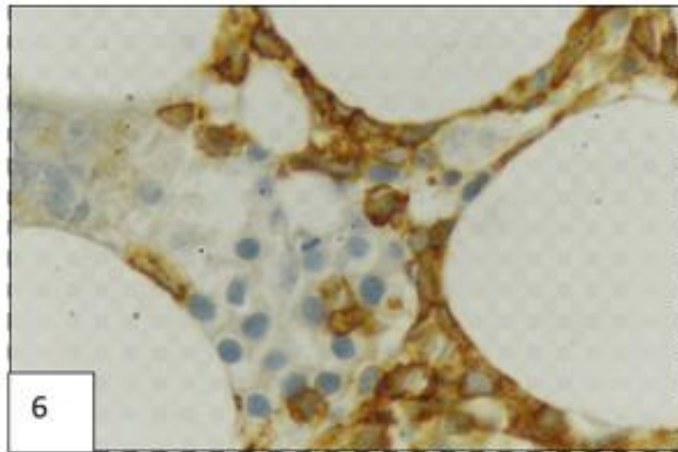


Fig. 6. CD 7 showing strong membranous positivity in blasts (1000x; IHC)

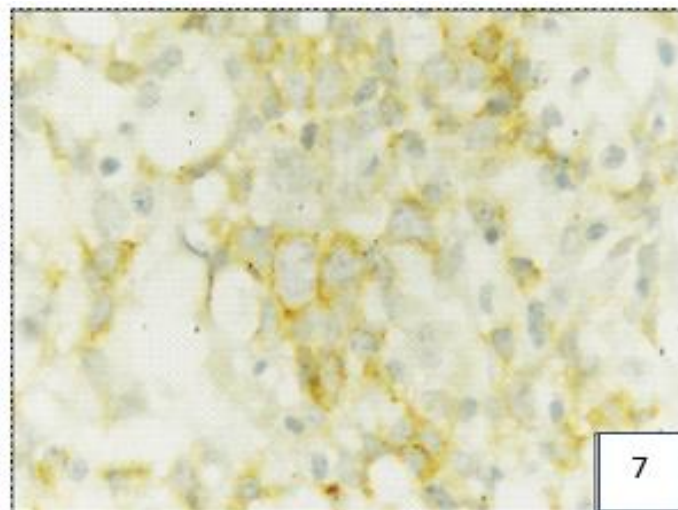


Fig. 7. CD 34 showing weak to moderatemembranous positivity in blasts (1000x; IHC)

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 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.

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.

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

3. 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 in the published english literature. 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. They found 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 factors such 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, collaborative efforts to gather and share data on this subtype are crucial for advancing research and enhancing patient care.

4. 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 clinical management recommendations are challenging because of the incomplete understanding of this entity's clinical and prognostic characteristics.

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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).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Naseem S, Sehgal T, Kumar N, Varma N, Das R, Ahluwalia J, et al. Hypocellular acute leukemia: Study of clinical and hematological features. *J Hematopathol*. 2014 Dec;7(4):147–52. DOI: 10.1007/s12308-014-0219-y
2. Jain D, Singh T, Kumar N. Hypocellular acute myeloid leukemia with bone marrow necrosis in young patients: Two case reports. *J Med Case Reports*. 2009 Dec;3(1):27. DOI: 10.1186/1752-1947-3-27
3. Needleman SW, Burns CP, Dick FR, Armitage JO. Hypoplastic acute leukemia. *Cancer*. 1981 Sep 15;48(6):1410–4. DOI: 10.1002/1097-0142(19810915)48:6<1410::AID-CNCR2820480624>3.0.CO;2-4
4. Berdeaux DH, Glasser L, Serokmann R, Moon T, Durie BG. Hypoplastic acute leukemia: Review of 70 cases with multivariate regression analysis. *Hematol Oncol*. 1986;4(4):291–305. DOI: 10.1002/hon.2900040406
5. Kumar H, Buch A, Iqbal B, Kakrani A. Hypoplastic acute myeloid leukemia-M4: A rare case report. *Med J DY Patil Univ*. 2016;9(1):129. DOI: 10.4103/0975-2970.167987
6. Nagai K, Kohno T, Chen YX, Tsushima H, Mori H, Nakamura H, et al. Diagnostic criteria for hypocellular acute leukemia: A clinical entity distinct from overt acute leukemia and myelodysplastic syndrome. *Leuk Res*. 1996 Jul;20(7):563–74. DOI: 10.1016/0145-2126(95)00136-0
7. Tuzuner N, Cox C, Rowe JM, Bennett JM. Hypocellular acute myeloid leukemia: The rochester (New York) experience. *Hematol Pathol*. 1995;9(3–4):195–203.
8. Matloub YH, Brunning RD, Arthur DC, Ramsay NK. Severe aplastic anemia preceding acute lymphoblastic leukemia. *Cancer*. 1993 Jan 1;71(1):264–8.

- DOI: 10.1002/1097-0142(19930101)71:1<264::AID-CNCR2820710140>3.0.CO;2-8
9. Bennett JM, Orazi A. Diagnostic criteria to distinguish hypocellular acute myeloid leukemia from hypocellular myelodysplastic syndromes and aplastic anemia: Recommendations for a standardized approach. *Haematologica*. 2009 Feb 1;94(2):264–8. DOI: 10.3324/haematol.13755
10. Klingemann HG, Storb R, Sanders J, Deeg HJ, Appelbaum FR, Thomas ED. Acute lymphoblastic leukaemia after bone marrow transplantation for aplastic anaemia. *Br J Haematol*. 1986 May;63(1):47–50. DOI: 10.1111/j.1365-2141.1986.tb07493.x
11. Laishram R, Punyabati P, Devi M, Khopey J. Hypoplastic acute myeloid leukemia-report of three cases. *Ann Trop Med Public Health*. 2014;7(1):61.
12. Quesenberry PJ, Rapoport JM, Fountebouni A, Sullivan R, Zuckerman K, Ryan M. Inhibition of normal murine hematopoiesis by leukemic cells. *N Engl J Med*. 1978 Jul 13;299(2):71–5. DOI: 10.1056/NEJM197807132990204
13. Beard ME, Bateman CJ, Crowther DC, Wrigley PF, Whitehouse JM, Fairley GH, et al. Hypoplastic acute myelogenous leukaemia. *Br J Haematol*. 1975 Oct;31(2):167–76. DOI: 10.1111/j.1365-2141.1975.tb00847.x
14. Nimubona S, Grulois I, Bernard M, Drénou B, Godard M, Fauchet R, et al. Complete remission in hypoplastic acute myeloid leukemia induced by G-CSF without chemotherapy: Report on three cases. *Leukemia*. 2002 Sep;16(9):1871–3. DOI: 10.1038/sj.leu.2402592
15. Lee M, Chubachi A, Niitsu H, Miura I, Yanagisawa M, Hirokawa M, et al. Successful hematopoietic reconstitution with granulocyte colony-stimulating factor in a patient with hypoplastic acute myelogenous leukemia. *Intern Med*. 1995 Jul;34(7):692–4. DOI: 10.2169/internalmedicine.34.692

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