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Case Report

Hypocellular AML versus MDS-diagnostic challenge case report with review of literature

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Abstract: Hypocellular AML being a rare entity with considerable overlapping features and characteristics with various other entities brings a need to have a better and clear understanding of hypocellular AML to differentiate in the decision-making process for therapeutic patient management. With some degree of dysplasia inherently associated with AML it is challenging to differentiate hypocellular AML from Myelodysplastic syndromes. We present a case report where the diagnostic dilemma in an elderly male patient who presented with fever, pallor, weight loss and fatiguability. On clinical examination, the patient had hepatomegaly. The patient was non-affording and was hence given supportive treatment, and he died soon after. Here the diagnostic dilemma is discussed along with the review of literature on hypocellular AML. A better and clear understanding of hypocellular AML is required to differentiate it from other entities due to the considerable overlap in presentation hence improving the decision-making process for therapeutic patient management. The shortcomings are realised, especially when the bone marrow cellularity is less than 10%. Our case report is written to enrich more understanding of the limited published literature on the subject.

Keywords: Hypocellular AML, myelodysplastic syndrome

Introduction

Acute myeloid leukemia (AML) is a group of hematopoietic cell malignancies derived from myeloid precursor cells. In these groups of hematopoietic cell malignancies, hypercellular bone marrow is usually observed, and hypocellularity is infrequently seen because of the increased number of malignant cells. Among these, there are some rare entities called hypocellular AML [1].

Hypocellular AML accounts for 5-12% of all cases of AML and is mainly seen in the elderly age group [2]. Although cases have been reported in childhood and adolescence, but these occurrences were infrequent [1]. In addition, it is also noted that 50% of the hypocellular AML is composed of secondary AML with a history of previous hematologic disorder or history of chemotherapy or radiotherapy [3].

Hypocellular AML is defined as bone marrow hypocellularity <20%, although some earlier reports considered less than 40% or 50% as hypocellular. Hypocellular AML is challenging to diagnose because the overlapping feature of hypoplasia in the marrow are also seen in other conditions like hypocellular myelodysplastic syndrome and aplastic anemia. There have been experiences in the past when a case diagnosed as MDS based on cytogenetics results turns out to be AML with recurrent cytogenetic abnormality. Also, the similar clinical features and lack of prompt investigations are often challenging to clinicians [4, 5]. We report a rare case of hypocellular AML in a 56-year-old male encountered in our institution.

Case report

A 56-year-old previously healthy male patient presented with fever, which was mild, on and off for the past six months. The fever was initially low grade over two months and progressed to high-grade fever in the last month. In addition, the patient also had complaints of pallor, weight loss and progressive fatigability leading

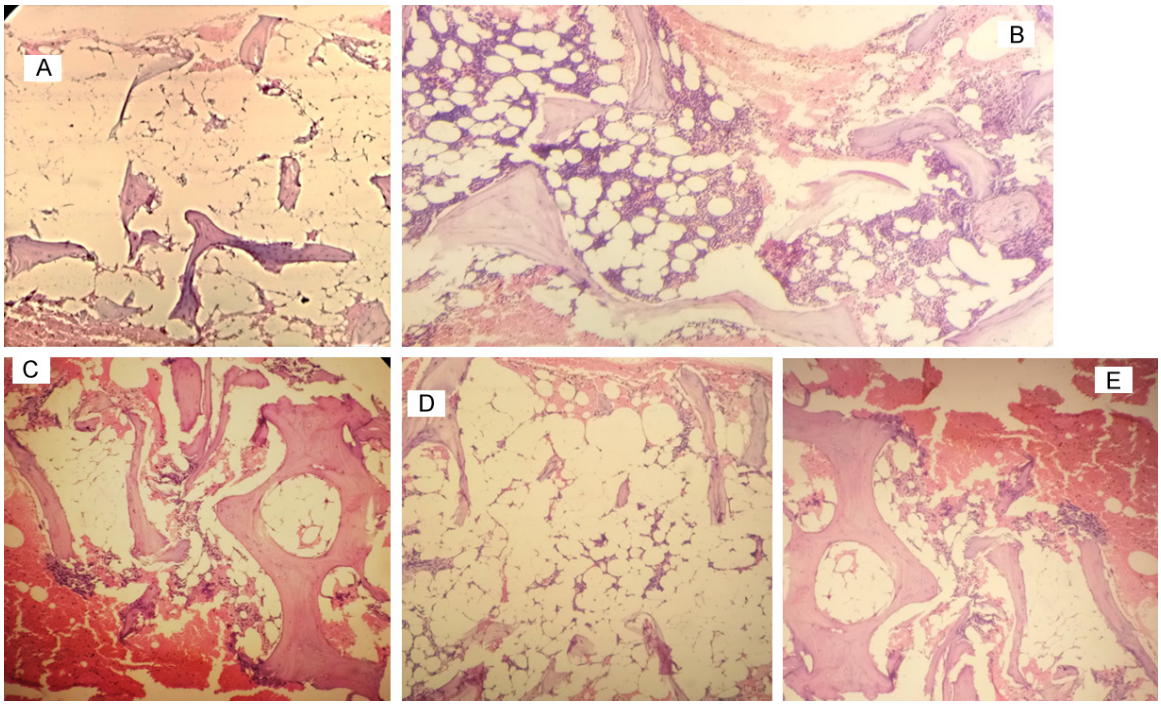


Figure 1. BM biopsy of Patient showing hypocellularity and presence of Blasts. A. Hypocellular region 4×, B. Normocellular focal area with predominantly lymphocytes and abnormal precursor cells 20×, C and D. Hypocellular areas 4×, E. A focal collection of abnormal precursor cells 4×.

to hospitalisation s on and off for the same period. On examination, pulse was 92/min, regular, BP 110/70, Pallor ++, no lymphadenopathy, clubbing, cyanosis, edema or icterus. P/A-Hepatomegaly was palpated 4 cm below the costal margin in the right midclavicular line, and splenomegaly was palpable at 3 cm below the costal margin.

Diagnosis

Lab investigations

On examination patient had Pancytopenia TLC: 3000/cu mm, Differential count of Polymorphs 10%, Lymphocytes-Monocytes-02%, Myelocytes-1% and Blasts 1%, Platelet count was 80,000/dl, and Hemoglobin was 7 gm%. There was evidence of Mild dyspoiesis in neutrophils, and suspicion of Myelodysplastic syndrome was made.

Serum biochemistry

Serum LDH was 1700 IU/L, LFT was mildly deranged, and USG abdomen showed non-fatty hepatomegaly.

Bone marrow examination

A bone marrow examination was done, and 16% blasts were identified in hypocellular marrow cellularity less than 10% for age. Bone marrow biopsy also confirmed similar findings **Figure 1**.

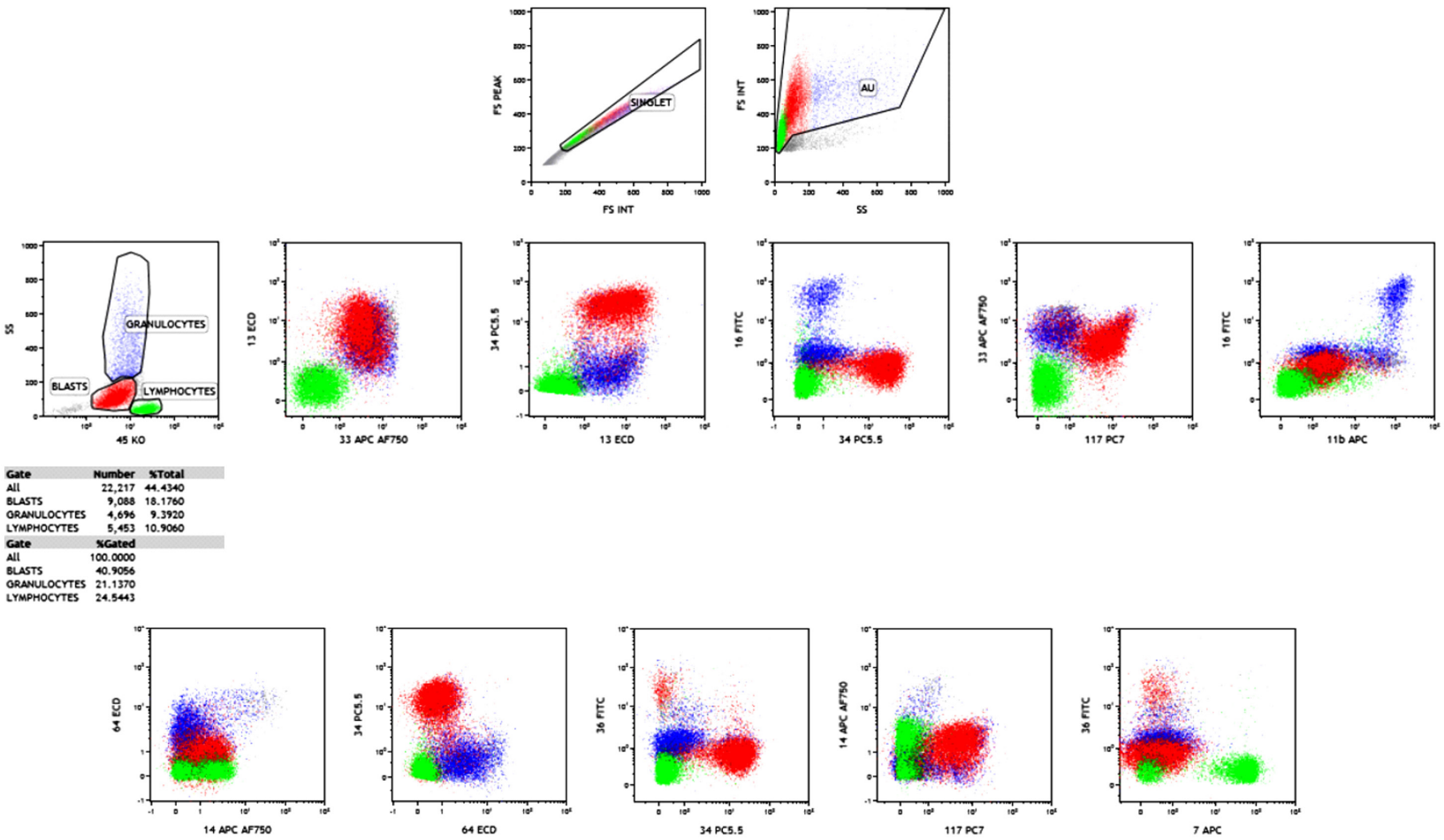
Immunophenotyping

Flowcytometry suggested the blasts (18% of the maximum gated population) to be of myeloid origin, as shown in **Figure 2** (CD34+, CD33+, CD13+, CD117+). A Cytogenetics panel was outsourced for the patient and revealed normal karyotype and no chromosomal abnormality.

Hence based on the above laboratory investigations, the patient was diagnosed with AML and lack of chromosomal abnormality excluded MDS.

Patient outcome

The patient refused treatment due to financial constraints and was given supportive treat-



Gate	Number	%Total
All	22,217	44.4340
BLASTS	9,088	18.1760
GRANULOCYTES	4,696	9.3920
LYMPHOCYTES	5,453	10.9060

Gate	%Gated
All	100.0000
BLASTS	40.9056
GRANULOCYTES	21.1370
LYMPHOCYTES	24.5443

Figure 2. Flowcytometry of BM sample of Patient showing (18% of the maximum gated population) to be of myeloid origin CD34+, CD33+, CD13+, CD117+.

ment to control infections and pancytopenia. The patient succumbed to death after six months of diagnosis.

Discussion

In our experience, diagnosis of hypocellular AML is based on pancytopenia and microscopic examination of both peripheral blood film and bone marrow by counting 100 cells and 500 cells, respectively [5]. However, in our experience, these features are also seen in MDS, where presentation and clinical characteristics are alike. The examination exhibits less than 20% bone marrow hypocellularity in contrast to the hypercellularity seen in the more common non-hypocellular AML. Also, the degree of dysplasia extends to other lineages in MDS like megakaryocytes and Erythroids except in MDS-RCUD, MDS with Unilineage Dysplasia. With many differences being discussed below, Al-Kali et al. showed that there are also some similarities in terms of cytogenetic and molecular characteristics between hypocellular AML and non-hypocellular AML, except for the low frequency of RAS and FLT3 mutations in the former entity [3].

The pathogenesis of hypocellularity is unclear; literature suggests some possible mechanisms may be involved. One such proposal was that the leukemia cell population inhibit myelopoiesis through a humoral mechanism [6]. Another proposal stated that myeloid precursors had increased susceptibility to different inhibitors in the older patient group [5, 7].

In our experience, in addition to microscopic examination, other findings from iron, immune staining of bone marrow biopsy, flow cytometry and cytogenetics were also helpful for differentiating these features, except in a few cases where immunophenotypic abnormalities on flow cytometry can overlap. The gold standard in these cases for exclusion of diagnosis is cytogenetics for complex karyotype. The most important feature from the above-mentioned examinations of hypocellular AML is the number of blast cells, which is >20% in these cases, except in cases of MAL with recurrent cytogenetic abnormalities that can easily be detected by identification of fusion transcripts. The authors feel that cases where the blast percentage is low, can also be confirmed by flow cytometry by correlating with the CD34 percentage. Still, caution should be undertaken for the changes influenced by haemodilution and other factors related to the specimen collection. Antibodies such as CD34 along with CD117, myeloperoxidase, lysozyme and CD68 are also utilised in immunohistochemical studies.

Even though there are some unique features for hypocellular AML, there is also an overlap of many symptoms and features with other entities like MDS and aplastic anemia. In our case clinical history of an elderly patient favoured MDS. For example, identifying two or more clusters of immature precursors with a minimum of at least three blasts per cluster was indicative of either MDS or AML. Likewise, erythroid dysplasia and megakaryocytic abnormalities (multinucleation, hypolobulation, abnormal clustering etc.) are seen both in AML and MDS. Still, it most likely suggests MDS, especially in the presence of >1 to 20% blast.

Furthermore, in our experience, normal or reactive marrow blasts are usually scattered near bone trabeculae or blood vessels. In contrast, in leukemic disorders, they form aggregates or clusters in the central marrow cavity. These islands stain strongly positive for immune markers of myeloid blasts. Sometimes these can be present in pre-malignant diseases, defined as abnormally localised immature myeloid precursor cells (ALIP), suggesting an aggressive MDS rather than AML. Some published literature like Bennet et al. have attempted to put forward some features and guidelines to differentiate these cases. However, case studies of these entities are still limited in literature and need further studies to improve these guidelines [5].

In terms of treatment and management, complete remission can be obtained with standard induction and intensive supportive treatment protocols, thereby decreasing the patient's mortality and morbidity [3]. Nonetheless, the prognosis of hypocellular AML remains poor, especially in elderly patients, because of the high relapse rate and infectious complications due to pancytopenia [1].

In summary, the study of various literature brings us to a consensus that hypocellular AML present with prominent cytopenias, older age, a history of the antecedent hematologic

disorder or prior chemotherapy/Radiotherapy and with low frequency of proliferative mutations. Furthermore, it shows the microscopic finding of low bone marrow cellularity (<20%), lack of dysplastic features in erythroid, myeloid, and megakaryocytic series and blast count of more than 20% in accordance with flow cytometry can aid us in confirming the diagnosis of hypocellular AML [3, 5].

Conclusion

In conclusion, as in our case, hypocellular AML being a rare entity with considerable overlapping features and characteristics with various other entities brings a need to have a better and clear understanding of hypocellular AML to differentiate and in the decision-making process for therapeutic management of the patient. The shortcomings are realised, especially when the bone marrow cellularity is less than 10%. Our case report is written to enrich more understanding of the limited published literature on the subject.

Disclosure of conflict of interest

None.

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