Case Report

DOI: 10.7860/JCDR/2022/56765.16749

Pathology Section

Unusual Presentation of Aplastic Anaemia: Evolving into Myelodysplastic Syndrome with Excess Blasts 1 and Type III Paroxysmal Nocturnal Haemoglobinuria Clone

SHILPI MORE[1], SAROJ RAJPUT[2], GEETIKA SHARMA[3], NIMISHA SHARMA[4], TATHAGATA CHATTERJEE[5]

ABSTRACT

Aplastic Anaemia (AA) is an immune mediated, primary haematopoietic disorder characterised by pancytopenia with significant morbidity and mortality. Allogeneic Haematopoietic Stem Cell Transplant (HSCT) is the treatment of choice in younger patients whenever Human Leucocyte Antigen (HLA) matched donor is available. For older patients and those in whom matched donor is not available, immunosuppressive therapy is the frontline treatment. With the long survivals of AA patients, clonal evolution into Myelodysplastic Syndrome (MDS) and clinically evident Paraoxysmal Nocturnal Haemoglobinuria (PNH) is frequently seen over a period of 5-10 years. The prognosis and overall survival of post AA, MDS is poor and the only treatment of choice is Allogeneic HSCT. The overall survival of post AA, MDS is however comparable to de novo MDS post-transplant. The authors hereby discuss a case of 26-year-old male patient, known case of AA who evolved into MDS with Excess Blasts 1 (MDS-EB-1) and type III PNH clone over a period of six years.

Keywords: Haematopoietic stem cell transplant, Human leucocyte antigen, Immunosuppressive therapy, Pancytopenia

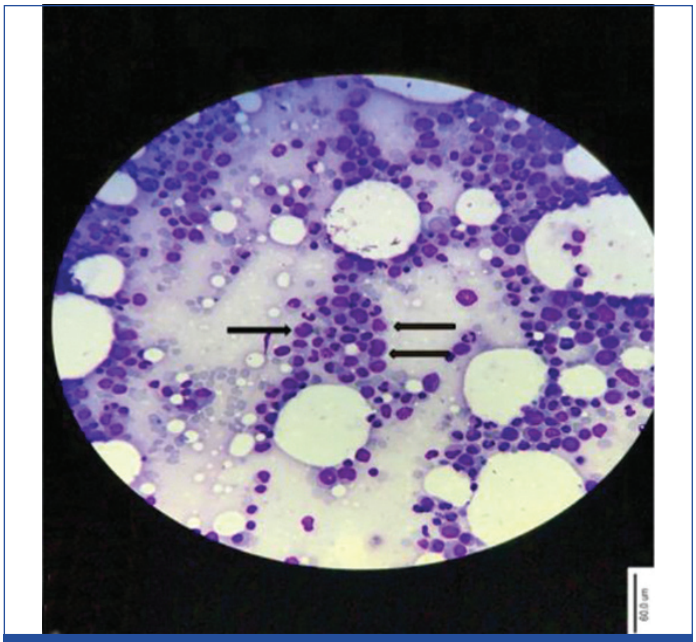
CASE REPORT

A 26-year-old male patient, known case of Aplastic Anaemia (AA), diagnosed at All India Institute of Medical Sciences (AIIMS), New Delhi in April 2014, presented with weakness and fatigability in September 2021. In 2014, patient had pancytopenia with haemoglobin of 6.1 g/dL, Total Leucocyte Count (TLC) of 3000/mm^3 and platelet count of 70,000/mm^3. Bone Marrow Biopsy (BMB) showed a patchy cellularity of 15-20% with increased lymphocytes and plasma cells. Patient received Immunosuppressive Therapy (IST) with cyclosporine and 20-25 units Packed Red Blood Cells (RBCs). He had an uneventful disease progression from year 2016-2019.

In January 2020, patient started having complaints of fatigability and weakness. He underwent Bone Marrow Aspirate (BMA) and biopsy in September 2020 which revealed patchy cellularity of 15-20% with increased lymphocytes and plasma cells. BMA revealed 2% blasts with myeloid to elytroid (M:E) ratio of 1:3 and increased iron deposition (Grade 4).

He eventually came to our hospital for allogeneic HSCT with a clinical diagnosis of AA in September 2021. He had a fully matched donor with 6/6 HLA matching from his sister. The authors advised a fresh BMA and BMB. His haemoglobin at this point was 3.7 g/dL, TLC was 2500/mm^3 and platelet count 13,000/mm^3. BMA was adequate with 50% cellularity and 7% blasts and M:E ratio of 2:1 [Table/Fig-1]. Dysmegakaryopoiesis was noted in the form of micromegakaryocytes and hypolobated megakaryocytes. BMB [Table/Fig-2] demonstrated similar findings with presence of blasts in the paratrabecular spaces, which showed membranous positivity for CD34 and membranous and cytoplasmic positivity for CD117 [Table/Fig-3,4]. Final impression was AA converted to MDS with excess blasts-1 (MDS-EB-1), World Health Organisation (WHO) 2016 classification [1].

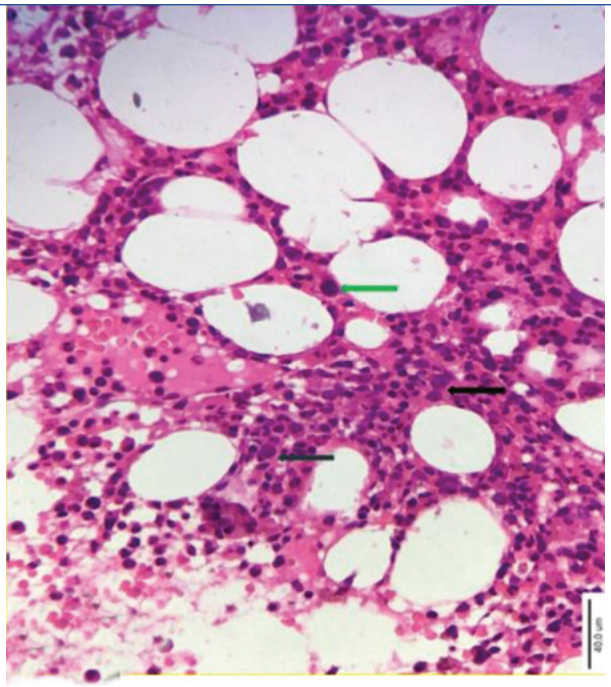
The authors also got Fluorescein-labeled proaerolysin (FLAER) test for detection of Paroxysmal Nocturnal Haemoglobinuria (PNH) clone and immunophenotyping by flow cytometer along with cytogenetics study for MDS. FLAER was positive for type III PNH



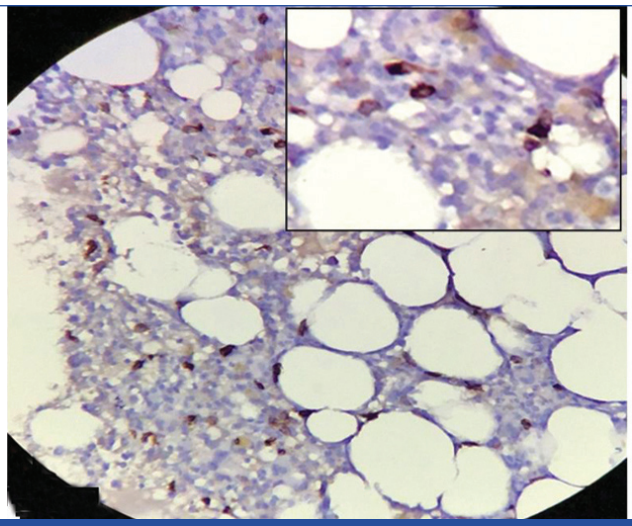
[Table/Fig-1]: Bone Marrow Aspirate (BMA) smears were cellular showing 50% cellularity with normoblastic erythroid maturation, myeloid series showing all stages of maturation with 7% blasts (highlighted by arrows) and M:E ratio of 2:1. (Leishman Giemsa, 400X).

clone. Flow cytometer revealed the blasts to be positive for Cluster of Differentiation (CD)45, HLADR, CD13, CD33, CD14, CD64, CD11b with aberrant expression of CD7 and cytoplasmic CD3 (cCD3). Cytogenetics by Fluorescence in-situ Hybridisation (FISH) showed positivity for deletion (del) 7q; del 5q, del 20q and trisomy 8 were found to be negative. Overall impression was AA converted into MDS-EB-1 with del 7q and type III PNH clone.

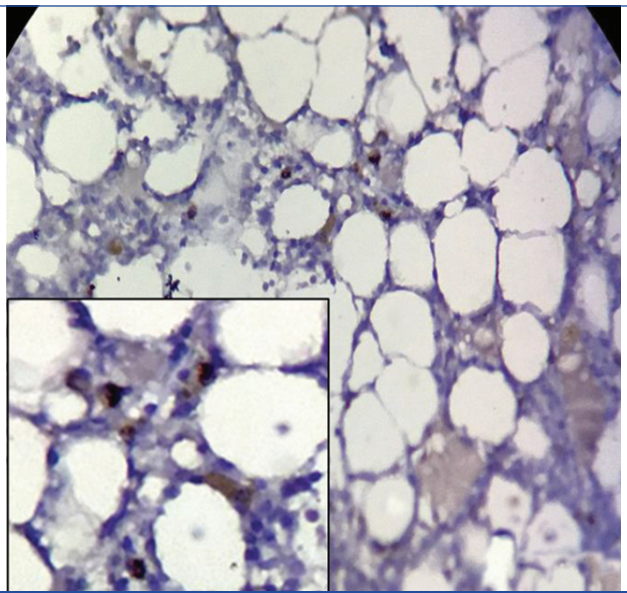
Patient was taken up for allogeneic HSCT with reduced-toxicity conditioning regimen with treosulfan, fludarabine and grafalon (ATG). He was transfused with stem cell harvest on day six with the CD34 dose being 6 million/Kg body weight. Daily hologram and



[Table/Fig-2]: Bone marrow biopsy (400X) showing cellular marrow with trilineage haematopoiesis. Blasts were seen as loose clusters in the paratrabecular areas, (highlighted by black arrows). Dysmegakaryopoiesis was seen in the form of hypolobated and micromegakaryocytes (highlighted by green arrow).



[Table/Fig-3]: On immunohistochemistry, the blasts are showing cytoplasmic and membranous positivity for CD117 (400X). Inset is highlighting the same at 1000X.



[Table/Fig-4]: On immunohistochemistry, the blasts are showing membranous positivity for CD34 (400X). Inset is highlighting the same at 1000X.

biochemical parameters were done. Patient received cyclosporine 150 mg twice a day and is under constant supervision and regular cyclosporine levels were monitored. He was engrafted on day 10 and it has been more than 100 days now post-transplant.

DISCUSSION

The patient in the present case report, was diagnosed with AA in 2014 at a young age of 19 years with a fully matched donor. After an uneventful duration of three years, there was clonal evolution into MDS. The case highlights the importance of early HSCT which has a five years overall survival approaching 82% in patients <20 years of age. This case also highlights the importance of identifying patients of AA, not responding to IST for early intervention and allogeneic HSCT even if a fully matched donor is not available. AA is an immune mediated, primary haematopoietic disorder characterised by pancytopenia with significant morbidity and mortality [2]. The incidence of AA is much more in South Asian countries compared to the West [3]. The main modalities of treatment for AA include optimised supportive treatment, Haematopoietic Stem Cell Transplant (HSCT) and IST. HSCT is the treatment of choice for paediatric and young patients whenever HLA matched donor is available. For older patients and patients in whom matched donor is not available, IST with cyclosporine or Anti-thymocyte Globulin (ATG), is the frontline treatment [4]. AA patients, especially the ones on IST are likely to show clonal evolution into MDS in 5-20% cases over a period of 5-11 years [5-7]. Association of AA with PNH clones is well established and clinically evident PNH is seen in 15-25% cases of AA [5,6]. With the long survival, the progression of AA to MDS has been reported to be 10-15% in some studies and 7% to Acute Myeloid Leukaemia (AML) within 10 years, especially those on IST. More than 50% cases of AA acquire PNH clones lacking surface Glycosylphosphatidylinositol (GPI)-linked proteins [5-8]. Recent data has shown genetic abnormalities in upto 50% patients with acquired AA, involving genes commonly mutated in myeloid malignancies [5].

The development of MDS/AML in AA is associated with a dismal prognosis and allogeneic HSCT is the only mode of treatment for such patients. Post AA, MDS patients behave similarly as de-novo MDS patients post-transplant with respect to overall survival, relapse rate and relapse free survival [9]. Cytogenetic is the only independent prognostic factor in both the group [9].

Approximately 3-26% AA patients show cytogenetic changes, of which numerical or structural abnormality of chromosome 7 is the most common, accounting for almost 40% [10]. In the setting of AA, monopsony 7 is associated with worse prognosis and poor response to IST and increased progression to MDS, while del (13q) and trisomy 8 are associated with an improved response to IST and a better prognosis [5,8]. In the presently discussed case, deletion 7q was detected which is associated with poor response to IST and increased rate of progression to MDS. However cytogenetic studies were done after evolution into MDS and not when primary diagnosis of AA was made. The pathophysiology of MDS as clonal evolution in AA patients may be secondary to immune regulation, possibly heightened by IST and immunomodulators used during the disease course [6].

CONCLUSION(S)

Allogeneic HSCT is the only mode of increasing the patient survival for cases that have developed MDS/AML. Cytogenetic evaluation should be done in AA patients at the time of diagnosis itself as abnormalities in chromosome 7 are associated with poor prognosis.

REFERENCES

[1] Orazi A, Brunning RD, Hasserjian RP, Germing U, Thiele J. Who classification of tumors of Haematopoeitic and Lymphoid Tissues. Revised 4th ed. Lyon. International Agency for research on cancer; 2017. Chapter 6, Myelodysplastic Syndrome; p.113-14.

[2] Urbanowicz I, Nahaczewska W, Celuch B. Narrative review of aplastic anemia-the importance of supportive treatment. Annals of Palliative Medicine. 2021;10(1):694-99.
[3] Mahapatra M, Singh PK, Agarwal M, Prabhu M, Mishra P, Seth T, et al. Epidemiology, clinico-haematological profile and management of aplastic anaemia: AIIMS experience. J Assoc Physicians India. 2015;63(3 Suppl):30-35.
[4] Peslak SA, Olson T, Babushok DV. Diagnosis and treatment of aplastic anemia. Curr Treat Options Oncol. 2017;18(12):70.
[5] Ogawa S. Clonal hematopoiesis in acquired aplastic anemia. Blood. 2016;128(3):337-47.
[6] Afable MG, Tiu RV, Maciejewski JP. Clonal evolution in aplastic anemia. Hematology Am Soc Hematol Educ Program. 2011;2011:90-95.
[7] Sun L, Babushok DV. Secondary myelodysplastic syndrome and leukemia in acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria. Blood. 2020;136(1):36-49.
[8] Stanley N, Olson TS, Babushok DV. Recent advances in understanding clonal haematopoiesis in aplastic anaemia. Br J Haematol. 2017;177(4):509-25.
[9] Kim SY, Le Rademacher J, Antin JH, Anderlini P, Ayas M, Battiwalla M, et al. Myelodysplastic syndrome evolving from aplastic anemia treated with immunosuppressive therapy: Efficacy of hematopoietic stem cell transplantation. Haematologica. 2014;99(12):1868-75.
[10] Maciejewski JP, Risitano A, Sloand EM, Nunez O, Young NS. Distinct clinical outcomes for cytogenetic abnormalities evolving from aplastic anemia. Blood. 2002;99(9):3129-35.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, ESIC Medical College and Hospital, Faridabad, Haryana, India.
2. Senior Resident, Department of Immunohaematology and Blood Transfusion, ESIC Medical College and Hospital, Faridabad, Haryana, India.
3. Associate Professor, Department of Immunohaematology and Blood Transfusion, ESIC Medical College and Hospital, Faridabad, Haryana, India.
4. Associate Professor, Department of Immunohaematology and Blood Transfusion, ESIC Medical College and Hospital, Faridabad, Haryana, India.
5. Professor and Head, Department of Immunohaematology and Blood Transfusion, ESIC Medical College and Hospital, Faridabad, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Tathagata Chatterjee,
Professor and Head, Department of Immunohaematology and Blood Transfusion,
ESIC Medical College and Hospital, Blood Bank, Faridabad, Haryana, India.
E-mail: ctathagat@hotmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 06, 2022
- Manual Googling: May 17, 2022
- iThenticate Software: Jul 11, 2022 (6%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Mar 30, 2022**
Date of Peer Review: **Apr 18, 2022**
Date of Acceptance: **May 19, 2022**
Date of Publishing: **Aug 01, 2022**