Successful Management of NPM1-Mutated Acute Myeloid Leukemia in a Patient with Robinow Syndrome

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Abstract

Robinow syndrome is a rare congenital disorder characterized by a range of phenotypically heterogeneous abnormalities. We present a successful management of acute myeloid leukemia (AML) in a 19-year-old man with Robinow syndrome. The patient presented with a high white cell count (WBC) of $402X10^9$/L at the time of diagnosis and very high peripheral blast count. Given the scarcity of reported AML cases in individuals with Robinow syndrome and potential concerns regarding the compatibility of chemotherapy with this syndrome, we report our experience to offer a reference for comparable cases in the future.

Keywords: AML, NPM-1, Robinow Syndrome, Hemivertebrae, Congenital.

Introduction

AML is a malignant disorder originating in the bone marrow, characterized by aberrant clonal expansion and differentiation arrest of myeloid progenitor cells.[1] According to the most recent SEER database, this condition accounts for 1.0% of all new cancer cases in the United States, affecting both men and women at a rate of 4.1 cases per 100,000 individuals annually[2]. NPM1 is notably the most mutated gene in adult AML seen in approximately 30% of cases.[3,4]

Case Report

A 19-year-old man with Robinow syndrome presented with a two-week history of generalized bone pain and fatigue. Initial blood work conducted at a local hospital revealed pancytopenia and leukocytosis with a total WBC of 390x10^9/L. His past medical history is remarkable for history of recurrent lung infections and asthma, with confirmed bronchiectasis changes evident in prior chest CT scans. The patient's only routine medication is Salbutamol as needed. His physical examination showed distinctive features including short stature with short limbs, macrocephaly, widely spaced eyes. Skeletal survey confirmed physical findings of short limbs [Figure 1].

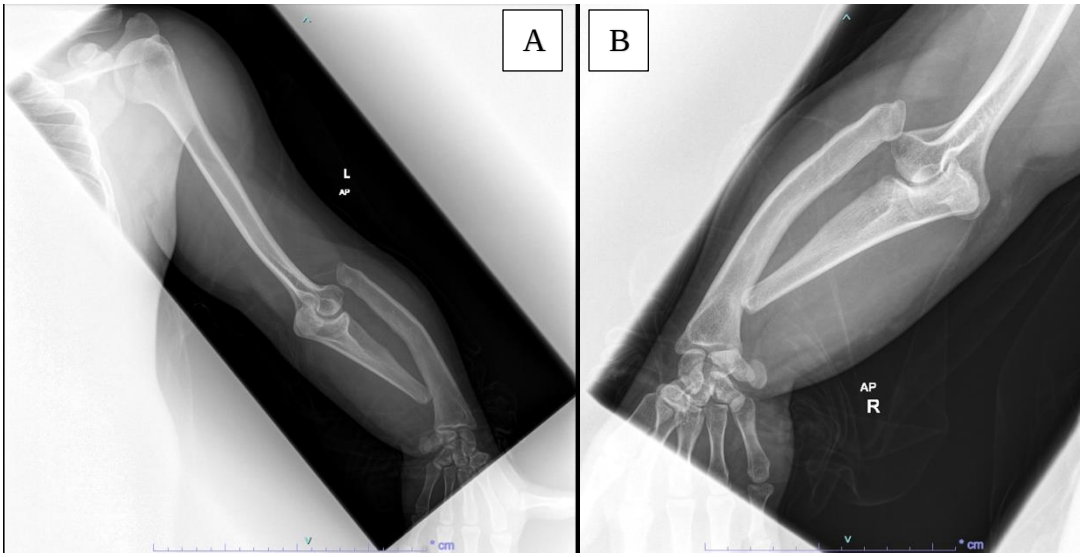

Figure 1: (A): Relative shortening of the humerus. Absent radial head with lack of radiocapitellar articulation. Absent distal ulna. (B): Absent radial head with lack of radiocapitellar articulation. Absent distal ulna.

Peripheral blood film showed marked leukocytosis with numerous circulating blasts accounting for 98% of his total WBC. These blasts are small to medium in size with high nuclear to cytoplasmic ratio, open chromatin, inconspicuous nucleoli and a thin rim of agranular greyish cytoplasm. No Auer rods. Blood work done upon admission to leukemia service summarized in Table 1.

Table 1: Summary of investigation upon admission to leukemia service.

Parameter	Result	Normal range
WBC	$402X10^9$	(2.4-9.5)
Blasts	$394.5x10^9$	
Hemoglobin (Hb)	9.6 g/dl	(11.0-14.5)
Platelet count	$83x10^9$ /L	(150-450)
absolute neutrophil count (ANC)	$4x10^9$/L	(1-4.8)
Potassium (K)	3.7 mmol/L	(3.5-5.1) mmol/L
Sodium (Na	139 mmol/L	(135-145) mmol/L
Lactate dehydrogenase (LDH)	299 U/L	(135 – 225) U/L
calcium (Ca)	2.25 mmol/L	(2.15 - 2.55) mmol/L
Phosphate	1.56 mmol/L	(0.81 - 1.45) mmol/L
Uric acid	0.30 mmol/L	(0.20 - 0.45) mmol/L

Bone marrow aspirate revealed similar blasts morphology to blood film. Flow cytometry results shown in Figure 2. Negativity for HLA-DR and CD34 expression on these blasts rose the possibility of acute promyelocytic leukemia (APL) although the morphology was not suggestive. Molecular for PML/RARA t(15;17) came back negative. Molecular testing for NPM1 came back positive. Cytogenetics revealed normal male karyotype 46, XY. Furthermore, FLT3-ITD testing was negative.

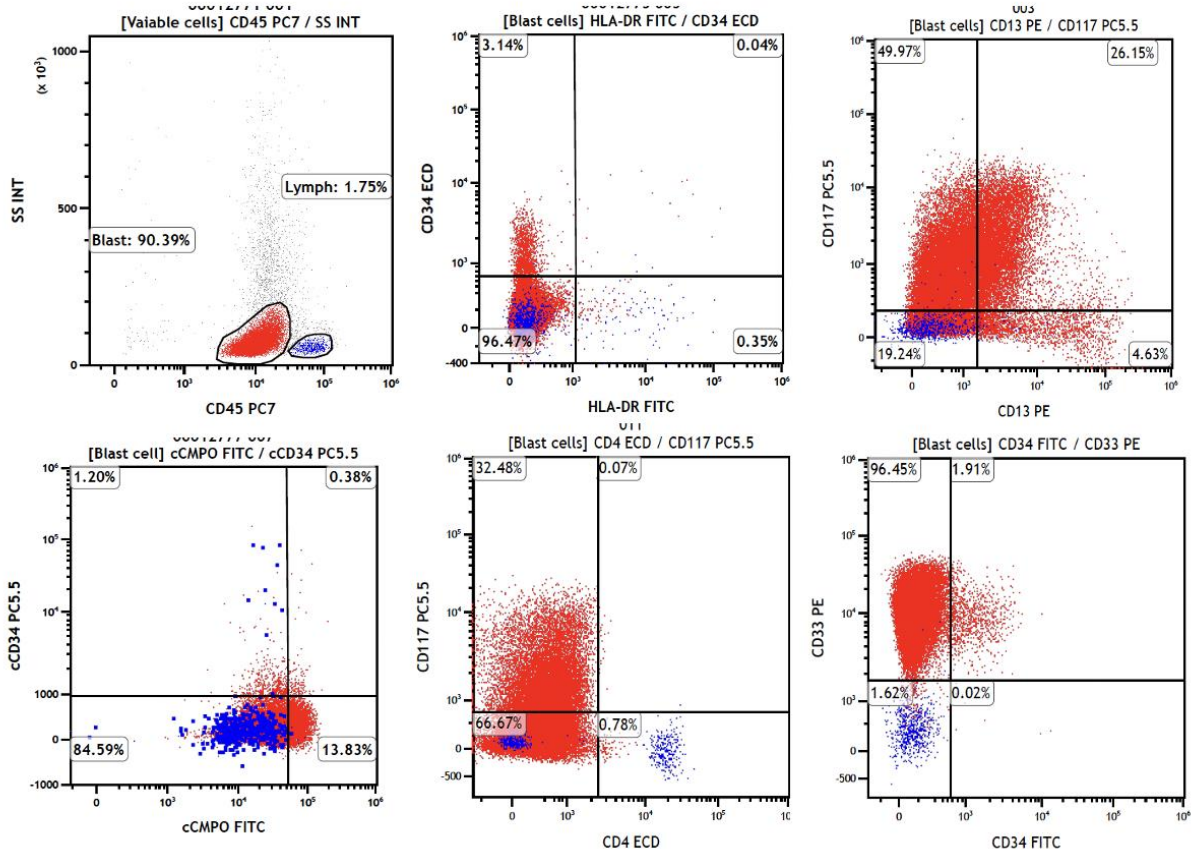

Figure 2: Flowcytometry from bone marrow aspirate. Red populating is blasts; blue population is lymphocytes. Flowcytometry showing abnormal cluster of blast cells, located at low to SSC with moderate CD45 expression accounting for around 90% of total events. Those blasts cells express: CD117+ ((Partial), CD13+ (Partial)+, CD11c+ (Partial), CD33+(Bright) and cyto MPO+. The same population was negative for surface CD34-, HLA-DR.

In view of known diagnosis of Robinow syndrome, detailed organ assessment was requested. An echo cardiogram was done pre-induction chemotherapy was normal, with estimated ejection fraction of 63%, No structural abnormalities identified. ultrasound abdomen revealed spleen size of 10 cm. Kidneys were of normal size, shape and position mild increased echogenicity, and no hydronephrosis.

Our patient underwent induction therapy with a 3+7 regimen (cytarabine 100 mg/m2 and daunorubicin 60 mg/m2) administered at full doses. Patient was also started on prophylactic Posaconazole 300 mg po daily as antifungal prophylaxis. Induction phase was complicated by culture negative febrile neutropenia. The patient's neutrophil and platelet counts recovered on D+23 of induction. A post-induction bone marrow biopsy confirmed morphological and molecular remission.

For consolidation therapy, the patient received HIDAC (high dose cytarabine 3g/m2) for total of three cycles. The first two consolidation cycles were complicated by episodes of febrile neutropenia and urinary tract infections. The final consolidation cycle was further complicated by perianal skin infection, leading to persistent high-grade fever. Patient underwent an examination under anesthesia as there was concern for a Fournier's gangrene in view of rapidly progressing skin redness and appearance of necrotic skin changes, this was fortunately ruled out intraoperatively, he required minor incision and drainage. Patient recovered very quickly from infection perspective upon neutrophil recovery.

At the conclusion of treatment, a bone marrow examination confirmed the ongoing morphological and molecular remission. The patient has been closely monitored with monthly molecular testing for NPM1, which consistently remained negative.

Discussion

NPM1 mutated AML was recognized as a distinct entity in 2017 WHO classification of myeloid neoplasms. On the updated European Leukemia Network (ELN 2022) classification for myeloid neoplasms, NPM1 mutated AML has been redefined as a distinct entity without FLT3 mutation.[5,6] Additionally, the diagnostic criteria for this condition have been revised, with a new threshold of >10% leukemic blasts required for diagnosis.[5,6] The NPM1 mutation holds a pivotal role as a "gatekeeper" mutation, significantly contributing to the initiation of leukemogenesis. The acquisition of these mutations appears to serve as a critical initial event that sets the stage for the subsequent development of full-fledged leukemia.[7,8]

NPM1 mutated AML is classified as favourable risk AML with estimated remission rates of 80% and overall survival of 40%.[9] It commonly presents with high blasts percentage and elevated WBC at the time of diagnosis and increased extramurally involvement.[7]

Consistent with the common presentation associated with NPM1 mutation, our patient displayed a remarkably elevated WBC reaching approximately $402x10^9$/L at the time of initial presentation. Fortunately, he did not manifest any symptoms indicative of leukostasis, and he responded promptly to cytoreduction with hydroxyurea. Moreover, there were no indications of extramedullary disease with negative CSF for blasts.

Robinow syndrome was initially documented in 1969 by Robinow et al. In their seminal work, they delineated a novel dwarfing syndrome characterized by mesomelic limb shortening, hemivertebrae, and genital hypoplasia[10]. Robinow introduced the term "fetal facies" to capture the distinctive facial appearance associated with the syndrome, a term that has persisted and continued to be employed in medical literature.

Medical literature now encompasses over 100 documented cases of Robinow syndrome, across wide range of ethnic groups. Clusters of cases have been observed in regions such as Turkey, Oman, and Czechoslovakia.[11] These occurrences are indicative of the pronounced level of consanguinity within these populations. Our patient is from Oman, his parents are first cousins, he has a sister with Robinow syndrome and additional 8 unaffected siblings.

There are two main distinct forms of Robinow syndrome, autosomal recessive and less severe autosomal dominant Robinow syndrome. These forms are differentiated by their modes of inheritance, symptomatic expression, and overall severity.[12,13]

In addition to the external features, there is also a notable description of renal tract abnormalities linked with the genital anomalies in Robinow syndrome. Hydronephrosis is relatively common and can potentially predispose individuals to urinary tract infections.[10] Cystic dysplasia of the kidney is another documented renal abnormality associated with this syndrome.[10]

Another significant anomaly linked to this syndrome is congenital heart disease, with an estimated prevalence of approximately 15% based on published cases.[10,14] Among the most frequently observed congenital heart issues are atrial septal defects (ASD), ventricular septal defects (VSD), coarctation of the aorta, tetralogy of Fallot, and the most prevalent abnormality being pulmonary stenosis or atresia.[10,15]

Our patient echo cardiogram was unremarkable for any structural cardiac abnormalities and has normal ejection fraction, it’s worth noting that most of the cardiac anomalies usually present within the first year of life. Our patient did however have recurrent urinary symptoms throughout the consolidation with two episodes of urinary tract infection. In term of tolerance to cytotoxic chemotherapy we did not observe any unusual complications in this case.

Febrile neutropenia remains a major challenge during induction chemotherapy in acute myeloid leukemia. Our patient has multiple episodes of febrile neutropenia during his treatment period. ICU-based care, nosocomial acquisition, female gender, and previous antibiotic therapy have been identified as risk factors for bacteremia caused by ESBL-producing E. coli[16]or resistant K. pneumoniae in patients with hematologic malignancies, mainly AML.[17] Furthermore, AML patients can be predisposed to developing invasive fungal infections due to various risk factors, including advanced age, pulmonary comorbidities, high-dose steroid treatment, duration of neutropenia, and relapse/refractory disease.[18,19] To address these concerns, our patient received prophylactic antimicrobial therapy during both induction and consolidation phases when their Absolute Neutrophil Count (ANC) dropped below 0.5x10^9/L. These preventive measures are crucial steps in mitigating infectious complications, particularly during the induction chemotherapy phase.

It's also worth mentioning based on our literature review there is no known direct correlation between Robinow syndrome and the development of AML.

Conclusion

Robinow syndrome represents a rare condition characterized by a distinct phenotype, often accompanied by recognizable renal and cardiac abnormalities. Managing AML within this unique population can pose challenges due to potential concerns about end-organ toxicities. In our patient's case, we did not encounter any unusual toxicities throughout the treatment journey, except for recurrent urinary tract infections. Notably, there were no cardiac or renal toxicities observed. Furthermore, we successfully administered the complete treatment regimen without encountering any adverse events or requiring chemotherapy dose adjustments in this patient. Conducting a thorough organ assessment is a crucial step prior to commencing chemotherapy.

Disclosure

The authors declare that they have no conflicts of interest. Consent for publication was obtained from the patient and his family.

References

1. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. Blood Rev 2019 Jul;36:70-87.

2. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2023 Apr 19. [updated: 2023 Jun 8; cited 2023 Aug 18]. Available from: https://seer.cancer.gov/statistics-network/explorer/. Data source(s): SEER Incidence Data, November 2022 Submission (1975-2020), SEER 22 registries. 2023.

3. Falini B, Brunetti L, Sportoletti P, Martelli MP. NPM1-mutated acute myeloid leukemia: from bench to bedside. Blood 2020 Oct;136(15):1707-1721.

4. Borer RA, Lehner CF, Eppenberger HM, Nigg EA. Major nucleolar proteins shuttle between nucleus and cytoplasm. Cell 1989 Feb;56(3):379-390.

5. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-19.

6. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 2022 Sep;140(12):1345-1377.

7. Sharma N, Liesveld JL. NPM 1 Mutations in AML-The Landscape in 2023. Cancers (Basel) 2023 Feb;15(4):1177.

8. Thiede C, Koch S, Creutzig E, Steudel C, Illmer T, Schaich M, et al. Prevalence and prognostic impact of NPM1 mutations in 1485 adult patients with acute myeloid leukemia (AML). Blood 2006 May;107(10):4011-4020.

9. Wang R, Xu P, Chang LL, Zhang SZ, Zhu HH. Targeted therapy in NPM1-mutated AML: Knowns and unknowns. Front Oncol 2022 Sep;12:972606.

10. Patton MA, Afzal AR. Robinow syndrome. J Med Genet 2002 May;39(5):305-310.

11. Suresh S. Robinow syndrome. Indian J Orthop 2008 Oct;42(4):474-476.

12. Roifman M, Marcelis CL, Paton T, Marshall C, Silver R, Lohr JL, et al; FORGE Canada Consortium. De novo WNT5A-associated autosomal dominant Robinow syndrome suggests specificity of genotype and phenotype. Clin Genet 2015;87(1):34-41.

13. Mazzeu JF, Pardono E, Vianna-Morgante AM, Richieri-Costa A, Ae Kim C, Brunoni D, et al. Clinical characterization of autosomal dominant and recessive variants of Robinow syndrome. Am J Med Genet A 2007 Feb;143(4):320-325.

14. Wabik AM, Skrzypczyk P, Dudek-Warchoł T, Warchoł S, Brzewski M, Pańczyk-Tomaszewska M. Nephrological and urological symptoms in patients with Robinow syndrome - a report of two cases. Pol Merkur Lekarski 2022 Oct;50(299):302-305.

15. Atalay S, Ege B, Imamoğlu A, Suskan E, Ocal B, Gümüş H. Congenital heart disease and Robinow syndrome. Clin Dysmorphol 1993 Jul;2(3):208-210.

16. Kang CI, Chung DR, Ko KS, Peck KR, Song JH; Korean Network for Study of Infectious Diseases (KONSID). Clinical predictors of Enterobacter bacteremia among patients admitted to the ED. Am J Emerg Med 2012 Jan;30(1):165-169.

17. Elgendy SG, Abdel Hameed MR, El-Mokhtar MA. Tigecycline resistance among Klebsiella pneumoniae isolated from febrile neutropenic patients. J Med Microbiol 2018 Jul;67(7):972-975.

18. Abdel Hammed MR, Elgendy SG, El-Mokhtar MA, Sayed D, Mansour SM, Darwish AM. T-lymphocytes Expression of Toll-like Receptors 2 and 4 in Acute Myeloid Leukemia Patients with Invasive Fungal Infections. Mediterr J Hematol Infect Dis 2022 Mar;14(1):e2022022.

19. Rambaldi B, Russo D, Pagano L. Defining Invasive Fungal Infection Risk in Hematological Malignancies: A New Tool for Clinical Practice. Mediterr J Hematol Infect Dis 2017 Jan;9(1):e2017012.