Successful T Cell Depleted Haploidentical Hematopoietic Stem Cell Transplant For a Novel NF-E2 Mutation Causing Inherited Thrombocytopenia

To the Editor:

Anderson Dik Wai Luk et al recently reported "NF-E2 mutation as a novel cause for inherited thrombocytopenia" in British Journal of Hematology where they reported novel NF-E2 mutation as a cause of inherited thrombocytopenia. Sanger sequencing identified the patient had a homozygous frameshift mutation (c.952delA, p.T318fsX326) in exome 3, which produced a truncated p45/NF-E2, with loss of its sumoylation site.[1] The patient was lost to their follow up thus the clinical course could not be ascertained. To our knowledge there is no literature on curative approach of thrombocytopenia due to this novel NF -E2 mutation. We present the first successful HSCT in a case of thrombocytopenia with a homozygous frameshift mutation of nuclear factor in exome 3, which produced a truncated p45/NF-E2. We got in touch with the author of the aforementioned correspondence and confirmed it's the same child who was lost to their follow up presented to us for further management.

17 months old male Filipino boy, 2nd in birth order, born as a result of non-consanguineous wedlock presented to Philippine General Hospital at 8 weeks of age with petechiae and purpura on face, trunk and extremities from day two of life, no history of bleeding from any other site and no other contributory finding on history or physical examination. He was extensively investigated in Philippines to look for any inherited or acquired causes of thrombocytopenia but unfortunately a clear-cut diagnosis was not established. Bone marrow examination revealed cellular marrow with trilineage haematopoiesis. He was empirically treated with intravenous immunoglobulin, prednisolone, cyclosporine, sirolimus; however, none was found to be effective and he remained on regular platelet and PRBC transfusions. Whole-exome sequencing (WES) was performed on the patient and his mother, which revealed the patient has a homozygous frameshift mutation in NF-E2 (c.952delA, p.T318fsX326), which resulted in a truncated transcription factor NF-E2 45 kDa subunit (p45/ NF-E2).[1] The mother was a carrier of the mutation. While the results of WES were awaited patient moved to UAE where both the parents were working and was at regular follow up at Dubai Hospital from where he was referred to us for

further management. He presented to us at 17 months of age for definitive management. Physical examination revealed petechiae and purpura on face, trunk and extremities and no evidence of bleeding from any other site. Systemic examination (BME) was unremarkable. After going thoroughly through his reports and reviewing the literature about NF-E2 mutation parents were counselled regarding the need of hematopoietic stem cell transplant (HSCT). In the absence of HLA matched sibling or unrelated donor, he was planned for T cell depleted (TCD) haploidentical transplantation. In view of BME showing erythroid hyperplasia and history of multiple transfusions in the past, we decided to give one course of pre-transplant immunosuppressive chemotherapy using fludarabine 150mg/m2 over 5 days, cyclophosphamide 1gm/m2 on day 1 and dexamethasone 20mg/m2/day in two divided doses for 5 days.[2,3] He was subsequently taken up for TCD haploidentical transplant using mother as donor (8/10 HLA compatible, donor specific antibody negative). Conditioning regimen consisted on fludarabine 30mg/m2/day D-7 to -3; Treosulfan 14g/m2/day from D-7 to -5; Thiotepa 10mg/kg in 2 divided doses on D-4 and ATG (Grafalon) 15mg/kg over 4 days in dose escalated manner.[4] Stem cells were collected from the donor after 5 days of GCSF and single dose plerixafor mobilization.[5] The graft was engineered using TCR αβ CD19 depletion (log reduction of 5.16 and 4.74 respectively) and CD34+ dose of 31.57x 10^6/Kg was infused to the recipient. Immediate post-transplant course was uneventful with neutrophil engraftment on day +11 and platelet engraftment on day +14. Whole blood chimerism on day +14 showed 97.94% donor DNA. Cytomegalovirus reactivation was noticed on day +38 (copy number 2307/mcl) which was successfully treated with ganciclovir followed by valganciclovir. Day +45 chimerism however dropped to 70% donor with hemogram showing falling platelets. Sirolimus was tapered over a week and stopped. Family was counselled regarding need of donor lymphocyte infusion (DLI). He received 3 doses of escalated DLI at 2 weekly intervals. His chimerism post 2nd DLI was 67% donor with improving platelet counts. Subsequently chimerism was repeated on day +100 and +150 which were 82.71% and 88.93% donor respectively. Patient is now day +356 post-transplant and is doing well clinically.

To best our knowledge, this is the first report of a curative approach for novel homozygous frameshift mutation in NF-E2 (c.952delA, p.T318fsX326), which resulted in a truncated transcription factor NF-E2 45 kDa subunit (p45/ NF-E2) manifesting clinically as inherited thrombocytopenia with hematopoietic stem cell transplantation. T cell depleted haploidentical transplant using TCR αβ CD19 depletion is a safe and effective way to treat the NF- E2 mutation related inherited thrombocytopenia.

Author contributions:

Contributions: GK conceptualized the protocol. ANB and AMR compiled the data. All the authors were involved in clinical care of the patient. All authors read and approved the final version of the manuscript.

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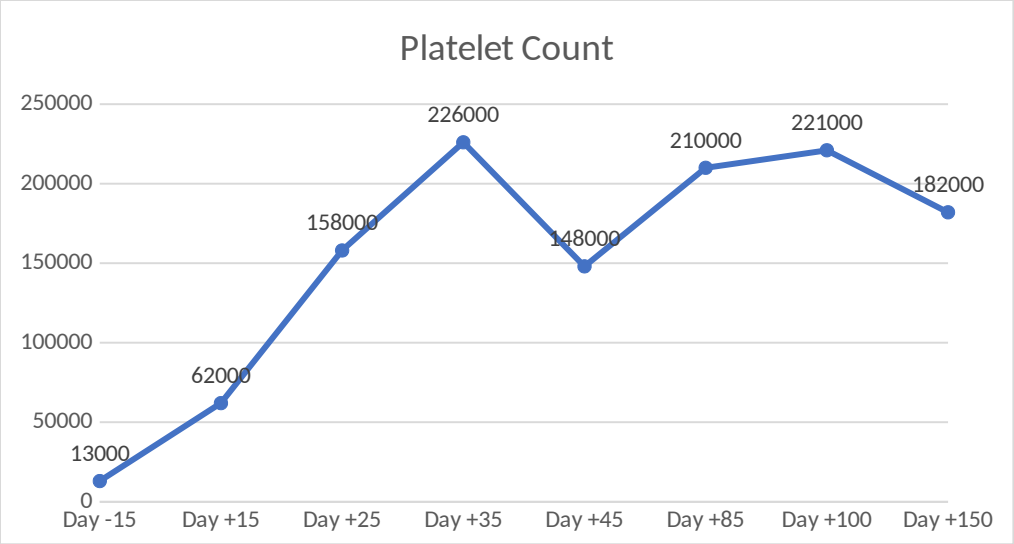
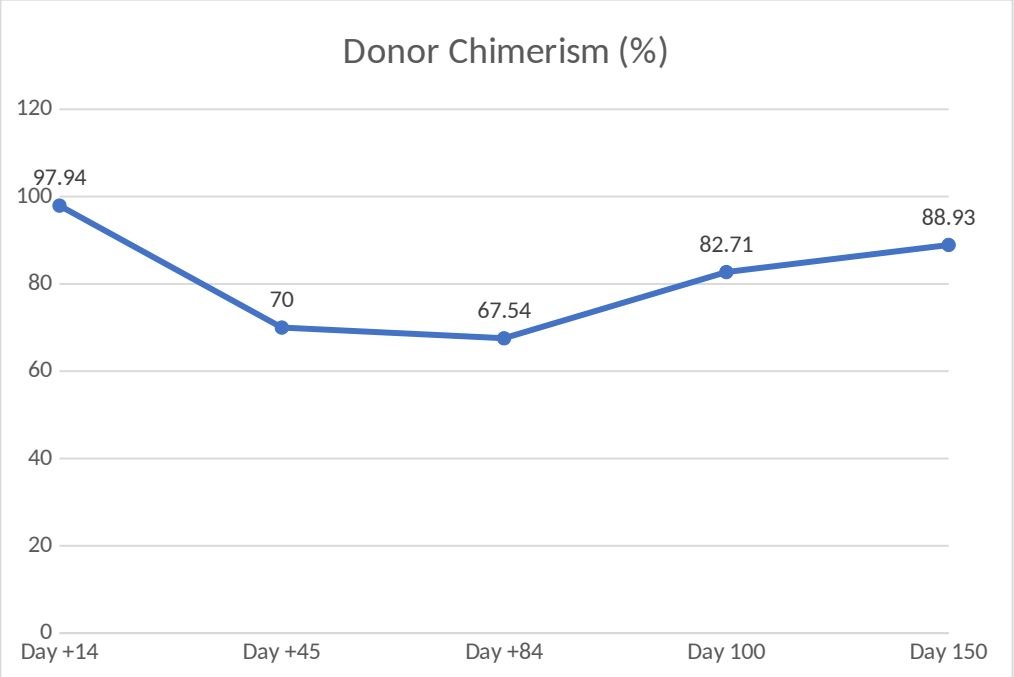
Supporting information:

Figure 1: Trend of platelets and donor chimerism





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