Transplant in Pediatric Hematology Oncology (TiP-HO)
Tumor Board Meeting Minutes (Thursday, 13th October, 2022)

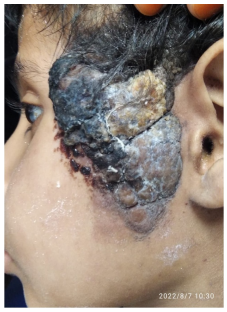
Discussion board during the last meeting (Alphabetical):

Name	Affiliation
Prof. Dr. Alaa El-haddad	Clinical Director of Pediatric Oncology and Stem cell transplant program Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Dalia Abdelaziz	Ass Professor of Pediatric Immunology Cairo University, Egypt
Prof. Dr. Hanafy Hafez	Consultant of Pediatric Hematology/Oncology & Stem cell transplant Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Ibrahim Abdelkader	Consultant of pediatric Hematology and Stem cell transplant Children's Mercy Hospital, Kansas City. University of Missouri-Kansas City School of Medicine. USA
Prof. Dr. Ibraheem Abosoudah	Consultant of Pediatric Hematology/Oncology and Stem cell transplant. King Faisal Specialist Hospital Research Centre, Jeddah, Saudi Arabia
Dr. Khaled Seddik	Ass Consultant of Pediatric Hematology/Oncology Borg Alarab Hospital, Alexandria University, Egypt
Prof. Dr. Leslie Lehmann	Clinical director of the Stem Cell Transplantation Program Dana-Farber/Boston Children's Cancer and Blood Disorders Center
Prof. Dr. Mahmoud Hammad	Consultant of Pediatric Hematology/Oncology & Stem cell transplant Children's Cancer Hospital (CCHE-57357) National Cancer Institute, Cairo University, Egypt
Prof. Dr. Nesrin Radwan	Ass Professor of pediatric allergy, immunology and rheumatology, Ain Shams University, Egypt Consultant of Pediatric Immunology, Children's Cancer Hospital (CCHE-57357)
Dr. Nessma Mahmoud	Pediatric Oncology Fellow Children's Cancer Hospital (CCHE-57357)

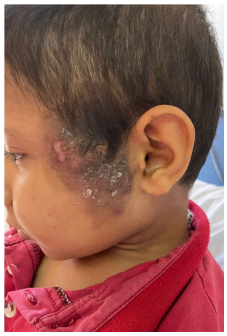
List of participating Centers

1. Children's Cancer Hospital (CCHE-57357), Egypt
2. National Cancer Institute, Cairo University, Egypt
3. Faculty of Medicine Ain Shams University, Egypt
4. Air Force Specialized Hospital, Egypt
5. South Egypt Cancer Institute, Assiut university, Egypt
6. Shefaa El Orman Oncology Hospital (SOH), Luxor, Egypt
7. Dar el Salam Cancer Hospital (Harmal Hospital), Cairo, Egypt
8. Borg Alarab Hospital, Alexandria, Egypt
9. Dana-Farber/Boston Children's Cancer and Blood Disorders Center, United States
10. Sultan Qaboos University Hospital, Muscat, Oman
11. Prince Sultan Military Medical City (PSMMC), Saudi Arabia
12. King Saud Medical City, Riyadh, Saudi Arabia
13. King Faisal Specialist Hospital Research Centre, Jeddah, Saudi Arabia
14. Newcastle Upontyne Hospitals NHS Foundation Trust, United Kingdom
15. Chlidren Hospital, Pakistan
16. Agha Khan University Hospital, Pakistan
17. Meenakshi Mission hospital, India
18. Royal Hospital, Oman
19. MD Anderson cancer Center, USA

Case 1— Blastic Plasmacytoid Dendritic Cell Neoplasm , Indications of Transplant?



- 12 years old male patient
- His condition started 7 months before presentation with left side facial nodule that resolved with antibiotics then reappeared again and resolved with steroids
- Presented to the hospital in 7-2022 with reappearance of the facial lesion
- **US and CT** showed: subcutaneous soft tissue lesion 3 cm in the left temporal region
- **Initial CBC:** Hb 10.3 Platelets: 50 WBC 31000 ANC 17000 Blast 16%
- **BMA:** Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
  - **Positive for**: CD45, **CD123,** CD4, HLA-DR
  - **Negative for**: CD1a, **CD56**, other myeloid and lymphatic markers
- CSF: -ve
- **Management:**
  - MDT opinion was to treat with ALL-like protocol
  - Started Total XVI protocol 8-2022
  - With marked improvement of the skin and subcutaneous lesions



- **Evaluations:**
  - MRD day 15: positive 0.13 %
  - MRD end of induction: positive 0.11 %
- Then started consolidation and developed rt sided pleural effusion and generalized edema with the first HDMTX but the MTX level was low with normal UOP and creatinine
- The pleural effusion was drained and patient improved and discharged
- He is now on 2nd HDMTX
- **HLA matching:** no brothers or sister from the same parents

Questions raised by presenter (Dr. Khaled Seddik, Egypt)

- Role of BMT in this case?
- To proceed with HLA with brothers from a different mother (Haplo-SCT) ?

Tumor board recommendations:

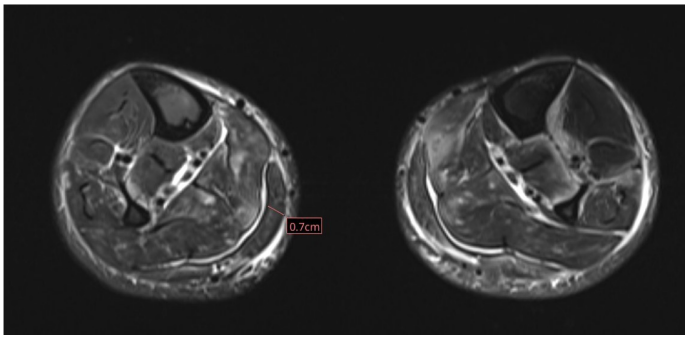
- A rare disease with few publications to get a solid conclusion however, longer remissions in BPDCN have been observed in adult patients with allo-HCT in first complete remission and lower survival have been reported in patients transplanted in CR2
- Giving the patient age, skin involvement at presentation and persistent positive MRD at end of induction, transplant in CR1 is recommended
- In absence of a matched donor, haplo-identical transplant with post-transplant Cy is recommended
- TBI based conditioning is a valid option.

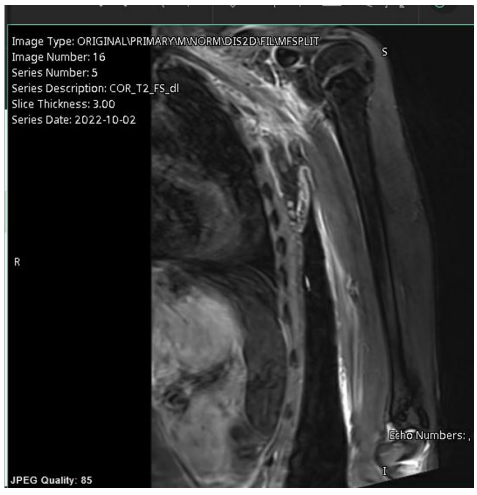
Scientific materials:

1. Marie Jeong-Min Kim, BHSc, Ahmed Nasr, MD, MSc, FRCSC, Bilaal Kabir, et al. **Pediatric Blastic Plasmacytoid Dendritic Cell Neoplasm: A Systematic Literature Review**, J Pediatr Hematol Oncol, 2017, DOI: 10.1097/MPH.0000000000000964
2. Qaiser Bashir, Denái R. Milton, Uday R. Popat, et al. **Allogeneic hematopoietic cell transplantation for patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)**, Bone Marrow Transplantation, 2022, https://doi.org/10.1038/s41409-021-01478-5
3. Mathieu Leclerc,1 R ´egis Peffault de Latour,2 Mauricette Michallet,3 et al, **Can a reduced-intensity conditioning regimen cure blastic plasmacytoid dendritic cell neoplasm?**, Blood, 2017, https://doi.org/10.1182/blood-2016-09-726653

Case 2: A Calf Pain in a Teen with PNH Undergoing MSD-SCT

- 16 yo patient with history of fatigue and dizziness for weeks presented to ER for acute abdominal pain in 4/2022
- **Past medical history**: positive for
  - ADHD/Tourettes
  - COVID in November 2021
- **CBC:** Hb 3 Plt 8 ANC 550 MCV 115
- **BMbx**: 15% cellularity, -ve for leukemia
- **BMF workup:** Negative except for **30% PNH clone**
- No thrombosis/active hemolysis
- The pt had a one **HLA matched brother**
- The patient was enrolled in a clinical trail with **Treosulfan** in the conditioning regimen (**Flu/Treo/ATG)**
- **Post-transplant supportive care:**
- **Day + 8:**
  - high grade fever and hypotension
  - Transferred to ICU
  - Blood culture was positive for **MSSA**
  - Received appropriate antibiotics, stabilized and became afebrile then transferred back to floor
- **2 days later:**
  - Point tenderness in his calf
  - US negative for clot
  - Afebrile
- **MRI lower extremity**:
  - Multiple intramuscular abscesses (bilateral soleus, lt ant. tibialis and lat. gastrocnemius muscle bellies)
  - Diffuse abnormal circumferential soft tissue swelling of the distal forelegs
  - Abnormal interfacial fluid along the deep calf compartment
- **MRI Spine:**
  - Paraspinal muscular edema mainly in the lumber and thoracic areas likely reflecting myositis
  - Multifocal areas of enhancement within the paraspinal musculature
- Biopsy was declined at first for the fear of compartmental syndrome or seeding, the lesions were deeply seated, and the patient was clinically improving





Diagnosed as **Myositis Tropicans** (Pyomyositis)

- Suppuration within skeletal muscles from bacteremic seeding
- 1st described in tropics/now reported in immunocompromised pts globally
- S. aureus is the most common organism
- Quadriceps is the most common muscle

- **Management:**
  - Appropriate antibiotics
  - Drainage if necessary
  - CVL removal
- The patient is now afebrile, engrafted, on Cefipeme monotherapy
- Developed a new lesion that will be drained and biopsied by interventional radiology

Questions raised by presenter (Prof. Dr. Leslie Lehmann, USA)

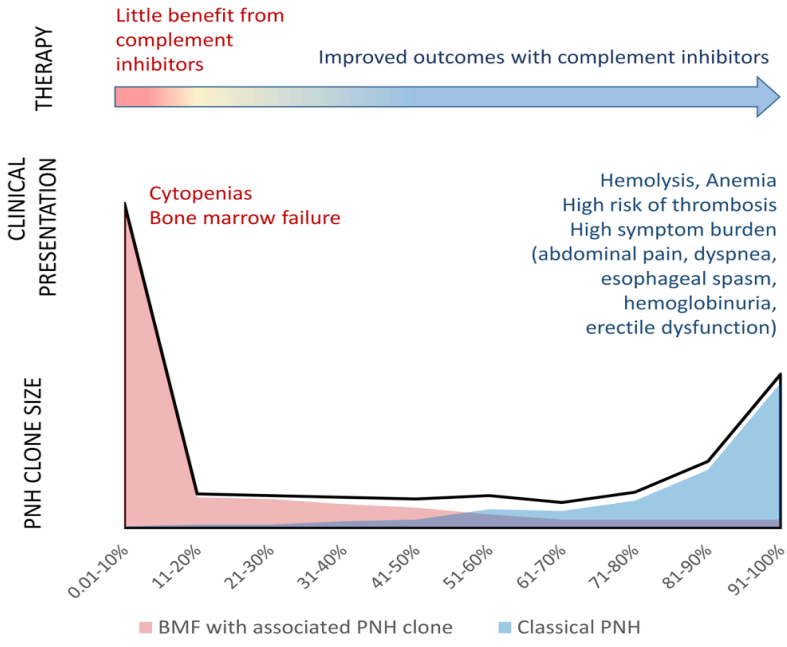
- What would have been the best therapy for this patient? HSCT with aplastic anemia conditioning, PNH MAC or Eculizumab therapy?
- Possible link between COVID and aplastic anemia?
- Recommendations for management of Myositis tropicans?
- Thoughts on Treosulfan conditioning?

Tumor board recommendations:

- Aplastic anemia with PNH clone needs a cut off level of ≥40% PNH clone is suggested to start having PNH symptoms
- In the absence of hemolysis, thromboembolic event and normal LDH levels the patient can be conditioned like aplastic anemia (non-myeloablative)
- Treosulfan based conditioning is associated with less side effects so far based on the European experience
- Identification of the causing organism is the mainstay of management of systemic abscesses so the board recommends following the biopsy results and treat accordingly

Scientific materials:

- Daria V. Babushok, **When does a PNH clone have clinical significance?**, Hematology Am Soc Hematol Educ Program (2021), https://doi.org/10.1182/hematology.2021000245
- S Chauhan, S Jain, S Varma, et al, **Tropical pyomyositis (myositis tropicans): current perspective**, BMJ, Postgrad Med J. 2004, doi: 10.1136/pgmj.2003.009274



Case 3: Burkitt's Leukemia with Underlying Immunodeficiency (KRAS & PIK3CD Mutations)

- 2 years old male presented to CCHE-57357 in 30/1/2019
- Presented with fever for 3 weeks not responding to antibiotics
- CBC was done which Revealed anemia, thrombocytopenia then patient referred to CCHE
- Steroids were given (many times during the 3 weeks before presentation)
- **Past medical history:**
  - Repeated chest infections and gastroenteritis since birth with failure to thrive
  - Repeated hospital admissions
  - History of blood products transfusions (2 times blood and 2 times platelets transfusion one week before presentation to CCHE)
- **Clinically:**
  - Constitutional: fever, night sweats, marked weight loss
  - Lymphatics: lower left cervical lymph nodes (larges 1.5 * 2 cm by physical exam)
- **Family history:**
  - Negative consanguinity and no family history of cancer
  - Siblings: 2 healthy (one male and one female)
- **Initial work up:**
  - Age: 2 years
  - CBC: TLC 4.6 Hb 10 Plts 19 P. blast 6%
  - ESR: 62/99 LDH: 3401 Virology PCR: Negative
  - BMA: ALL L2 61% blasts
  - IPT: Common ALL
    - Positive: CD19, CD79a, CD22, CD10, CD20 het , MHC Class II, Tdt
    - Negative: CD34, Cyt u, Kappa & Lambda, T & myeloid markers
    - Because of the high FSC & SSC; C myc is recommended
  - DNA Index: 1.269
  - Molecular: Negative
  - CSF: Traumatic without Blast
  - Chest X-Ray: Free
  - Abdomen US: HSM, liver 5 4 cm spleen 4 cm
- Diagnosed as C-ALL at first then cytogenetics revealed translocation (8;14) involving the cMYC gene
- **Final diagnosis**: Burkitt's leukemia, CNS Negative
- Started LMB Protocol group C on 3/2019 and ended TTT on 1/2020
- **Evaluations:**
  - BM cleared after 1st COPADM8
  - CTs post CYV II: Free
- **Supportive care during treatment:**
  - Developed lung nodules in 3/2019 during induction chemotherapy and started voriconazole for suspected aspergillosis
  - Stationary pulmonary nodules throughout treatment on voriconazole
  - Blood fungal PCR revealed candida albicans
  - Patient ended chemotherapy and yet presented with progressive lung damage so immunology consultation was done
- **Immunodeficiency work up done on 12/2020 revealed:**
  - Defective anti-tetanus antibody
  - CD19 of 18.4%=0.33mg/dl (non-functioning B-cell)
  - Memory cells of 5.97% and naive of 92%
  - Hypogammaglobulinemia

- **Immunology recommendations:**
  - For IVIG on a low dose every 2 month (0.4gm/kg) (last dose 8/2022)
  - For prophylactic Trimethoprim-Sulfamethoxazole & Levofloxacin
- **Gene sequencing was positive** for mutations in:
  - KRAS gene: heterozygous, AD
  - PIK3CD gene: heterozygous, AD
- **Final diagnosis:** *Activated PI3K-delta Syndrome with associated Burkitt's leukemia*
- As HSCT has been useful to treat lymphomas and life threatening infections in these patients, HLA matching was done
- His brother is one haplotype match
- **Current clinical status:**
  - Patient is clinically stable
  - He is doing fine off antibiotics
  - Still on IVIG / 2 months

Questions raised by presenter (Dr. Nessma Mahmoud, Egypt)

- Role of HSCT in this patient?
- Best Conditioning Regimen?

Tumor board recommendations:

- Based on the patient's history of repeated infections and the fact that he already developed malignancy, the patient is a candidate for HSCT
- MTOR inhibitors (Sirolumus) can be used as a bridge to transplant
- The donor should be screened for the mutations prior to transplant
- Haploidentical HSCT with post-transplant Cy using a reduced intensity conditioning regimen is recommended by the tumor board to avoid transplant related complications giving the patient's liability to severe toxicities
- IVIG should be given post-transplant until the patient is immune reconstituted

Scientific materials:

- Luigi D. Notarangelo, **Hematopoietic stem cell transplantation for activated phosphoinositide 3-kinase δ syndrome: Who, when, and how?**, J Allergy Clin Immunol. 2019, doi:10.1016/j.jaci.2018.08.039
- Romane Thouenon, Nidia Moreno-Corona, Lucie Poggi, et al, **Activated PI3Kinase Delta Syndrome—A Multifaceted Disease**, Frontiers in immunology, 2021, doi: 10.3389/fped.2021.652405
- Tanya I. Coulter and Andrew J. Can't, **The Treatment of Activated PI3Kδ Syndrome**, Frontiers in immunology, 2018, doi: 10.3389/fimmu.2018.02043

Treatment	Benefit in APDS	Proposed mechanism of action in APDS
Antimicrobial prophylaxis (e.g., Trimethoprim/Sulfamethoxazole or Azithromycin)	Reduction in respiratory tract infections	Prevention of respiratory bacterial infections
Immunoglobulin replacement therapy	Reduction in respiratory tract infections	Correction of antibody deficiency secondary to APDS
Haematopoietic stem cell transplantation	Reduction in respiratory & herpes infections Reduction in lymphoproliferation & autoimmunity	Replacement leukocytes effected by PI3Kδ hyperactivation
Sirolimus (Rapmycin)	Reduction in lymphoproliferation	Reduction in mTOR hyperactivation
Selective PI3Kδ inhibitors (e.g., Leniolisib)	Reduction in lymphoproliferation	Reduction in PI3Kδ hyperactivation

**** Activated phosphoinositide 3-kinase δ (PI3Kδ) syndrome (APDS)**

Our next TiP-HO meeting will be on Thursday November 3, 2022 (3-4 PM Cairo local time, GMT+2)
Whenever possible, please send your cases one week before the due date of our next meeting.
For further inquiries please do not hesitate to contact us

Best Regards
TiP-HO meeting coordinators

Prof. Dr. Mahmoud Hammad. Email: Mahmoud.hammad@nci.cu.edu.eg

Dr. Ahmed Obeid. Email: ahmedsalah@aun.edu.eg

Dr. Rana Helmi. Email: dr.ran.ahmed@gmail.com