ISPHO
34th Annual Conference of the Israeli Society of Pediatric Hematology Oncology (ISPHO)
Roxon Desert, Arad
May 2-4, 2024

Thursday, May 2, 2024

Session I - ONCOLOGY

Invasive Fungal Infections in Children with Acute Leukemia: Epidemiology, Risk Factors, and Outcome

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Invasive fungal infections (IFI) cause morbidity and mortality in children with acute leukemia (AL). We retrospectively collected data on febrile neutropenic episodes (FNE) in AL children (2016–2021) and assessed factors associated with proven/probable IFI. Ninety-three children developed 339 FNE. Seventeen (18.3%) children developed 19 proven/probable IFI (11 yeast; eight molds). The proven/probable yeast IFI rate was 6/52 (11.5%) in children who belong to the high risk for IFI category (HR-IFI-AL: high-risk acute lymphocytic leukemia (ALL), acute myeloid leukemia, relapse); and 5/41 (12.2%) in the non-HR-IFI-AL category (standard/intermediate risk ALL). The proven/probable mold IFI rate was 7/52 (13.5%) in HR-IFI-AL children and 1/41 (2.4%) in the non-HR-IFI-AL category. In the multivariable analysis, underlying genetic syndrome, oral mucositis, and older age were significantly associated with proven/probable IFI, while a longer time since AL diagnosis was protective. Two of 13 (15.4%) HR-IFI-AL children died because of IFI. The elevated risks of proven/probable mold IFI and the associated mortality in HR-IFI-AL children, and high risk of invasive candidiasis in the non-HR-IFI-AL group, emphasize the need for the close monitoring of local epidemiology and the adjustment of practices accordingly.

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A Need for a Novel Survival Risk Scoring System for Intensive Care Admissions Due to Sepsis in Pediatric Hematology/Oncology Patients

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Background: Children with hemato-oncological diseases or following stem cell transplantation (SCT) are at high risk for life-threatening infections; sepsis in this population constitutes a substantial proportion of pediatric intensive care unit (PICU) admissions. The current pediatric prognostic scoring tools to evaluate illness severity and mortality risk are designed for the general pediatric population and may not be adequate for this vulnerable subpopulation.

Methods: Retrospective analysis was performed on all PICU admissions for sepsis in children with hemato-oncological diseases or post-SCT, in a single tertiary pediatric hospital between 2008-2021 (n=233). We collected and analyzed demographic, clinical, and laboratory data and outcomes for all patients, and evaluated the accuracy of two major prognostic scoring tools, the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) and the Pediatric Risk of Mortality III (PRISM III).

Furthermore, we created a new risk-assessment model that contains additional parameters uniquely relevant to this population.

Results: The survival rate for the cohort was 83%. The predictive accuracies of PELOD-2 and PRISM III, as determined by the area under the curve (AUC), were 82% and 74%, respectively. Nine new parameters were identified as clinically significant: age, SCT, viral infection, fungal infection, central venous line removal, vasoactive inotropic score, bilirubin level, C-reactive protein level, and prolonged neutropenia. Unique scoring systems were established by the integration of these new parameters into the algorithm; the new systems significantly improved their predictive accuracy to 90% ($p=0.01$) and 87% ($p<0.001$), respectively.

Conclusions: The predictive accuracies (AUC) of the PELOD-2 and PRISM III scores are limited in children with hemato-oncological diseases admitted to PICU with sepsis. These results highlight the need to develop a risk-assessment tool adjusted to this special population.

Such new scoring should represent their unique characteristics including their degree of immunosuppression and be validated in a large multi-center prospective study.

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Alternaria Invasive Infection in Children with Hemato-Oncological Disease - A National Multicenter Report

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Background: Invasive fungal disease is a major cause of morbidity and mortality among hemato-oncology pediatric patients. While Aspergillus and Candida infections account for the majority of fungal infections, pediatric Alternaria infections are not well studied.
We aim to characterize the epidemiology, clinical manifestations, and outcome of this uncommon fungus in the pediatric hemato-oncologic population on a national basis.
Methods: This is a retrospective multi-centered observational study. The medical records of all children with proven Alternaria infection in the five largest tertiary pediatric centers during 2011-2023 were reviewed.
Results: During the 12-year study period 22 patients aged 4-18 years, were diagnosed with invasive Alternaria infection. Predominant underlying diagnoses were Acute Lymphoid Leukemia (55%) and Acute Myeloid Leukemia (23%). Ninteen patients (86%) presented with neutropenic fever. Clinical manifestations of Alternaria infection included invasive rhinosinusitis (77%), skin (14%), and pulmonary infection (9%). Most of the cases of invasive sinusitis (76%), exhibited suggestive complaints or physical findings. All skin lesions were described as ecthyma-like. Computed tomography corroborated all cases of suspected pulmonary infection, however, it demonstrated suggestive findings of sinusitis in only 47% of patients.
Treatment with voriconazole yielded a recovery rate of 90%, regardless of surgical involvement. Two fatalities were registered during treatment, both due to comorbidities and not the infectious episode.
Conclusions: This is the largest series of Alternatia infection in children to our knowledge. Most of the infections occurred in children with Acute Leukemia who presented with neutropenic fever. The study sheds light on the common clinical presentation, and reveals favorable prognosis, irrespective of the underlying disease.

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Re-exposure to High-dose MTX after Severe Delayed Elimination

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Introduction: High-dose Methotrexate (HDMTX) is used in most pediatric ALL protocols. Up to 4% of patients treated with HDMTX develop renal toxicity with severe delayed MTX elimination (DME). Most patients can be re-challenged with HDMTX but detailed information on the optimal dose and consequences is lacking and there are no evidence-based guidelines on re-exposure of patients to HDMTX after severe DME.
The purpose of our study was to investigate if re-exposure of patients to HDMTX after DME is tolerable, without severe toxicities.
Methods: As part of the PdL International Toxicity Working Group (PTWG), we collected data on ALL patients with severe DME events. DME events were prospectively captured as severe adverse events (SAEs) within the various national pediatric ALL protocols. Questionnaires regarding the HDMTX courses with DME including patients' clinical and laboratory data and re-exposure to HDMTX were completed by national investigators.
Results: The study cohort consisted of 209 children with DME from 12 countries. 163 children were re-exposed to HDMTX (82% of those scheduled for further MTX courses), and 77% (n=125) received multiple HDMTX courses. MTX dose during re-exposures ranged between 0.5-8 gr/m2 (64% received a full dose during the 1st and 80% during the 2nd re-exposure). The maximal creatinine levels were at a mean of 54 hours post-HDMTX (16-146), and the mean time to creatinine normalization was 4.4 Days (0-14). Sixteen patients had a 2nd DME event: 8 (5%) after the 1st re-exposure, 6 (4%) after the 2nd re-exposure, and 4 (2.5%) after the 3rd re-exposure. Three patients experienced multiple DME events. There were no other severe laboratory toxicities. Five patients suffered from severe mucositis and three from CNS toxicity. All toxicities after re-exposure were transient and without mortality.
Conclusions: Re-exposure to HDMTX after DME is safe and is not associated with severe toxicities.

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The Role of Check Point Inhibitors in Pediatric Primary Diffuse Leptomeningeal Melanomatosis: report of 2 cases

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Introduction: Primary diffuse leptomeningeal melanomatosis (PDLM), a subtype of malignant melanomas of CNS, is rare, especially in children. PDLM is defined by its characteristic diffuse invasiveness of the leptomeninges with or without nodules formation. Clinical manifestations of PDLM are nonspecific, mimicking the diagnosis of meningitis. As PDLM is neither sensitive to chemotherapy nor radiotherapy, the prognosis is extremely poor. Recently some new therapeutic aspects like immunotherapy, especially immune check point inhibitors (ICI) are emerging.

Cases report: First case: A 13 years old boy presented with 4 months of weakness, dysphasia and vomiting. MRI demonstrated diffuse leptomeningeal enhancement of the brain and spine. Brain biopsy confirmed the diagnosis of PDLM, with low PDL1 stains in immunohistochemistry, without targetable alterations on NGS. PET FDG normal. Treatment with ICI (Nivolumab 1 mg/gk/dose and Ipilimumab 3 mg/kg/dose, 4 courses every 21 days) was started. He developed severe complications after the 1st course (ICI enterocolitis and pancreatitis) and progressive disease after 2 courses. Craniospinal radiotherapy was deliverd at a dose of 30 Gy. The disease continued to progress, the patient died nine months after diagnosis.

Second case: A 7-year-old boy presented with diplopia, headache and vomiting. MRI demonstrated a cranial leptomeningeal enhancement and hypo-intense T1 and hyper-intense T2 signal at bilateral medial frontal cortex area. PET FDG normal. Brain biopsy confirmed the diagnosis of PDLM, with TMB 1.9, NRAS mutation and wild type BRAF by NGS. He started combination of ICI therapy. Three weeks after 1st course of Ipilimumab-Nivolumab he was admitted to PICU with prolonged status epilepticus. MRI demonstrated progression of leptomeningeal disease. Trametinib was deferred by parents and the child succumbed a year from diagnosis.

Conclusions: We report two cases of pediatric patients with PDLM treated unsuccessfully by immune check point inhibitors, emphasizing the diagnostic and therapeutic challenges in such a rare disease.

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Correction of T-Cell Repertoire and Autoimmune Diabetes in NOD Mice by Non-Myeloablative T-Cell Depleted Allogeneic HSCT

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The induction of partial tolerance toward pancreatic autoantigens in the treatment of type 1 diabetes mellitus (T1DM) can be attained by autologous hematopoietic stem cell transplantation (HSCT). However, most patients treated by autologous HSCT eventually relapse. Furthermore, allogeneic HSCT which could potentially provide a durable non-autoimmune T-cell receptor (TCR) repertoire is associated with a substantial risk for transplant-related mortality. We have previously demonstrated an effective approach for attaining engraftment without graft versus host disease (GVHD) of allogeneic T-cell depleted HSCT, following non-myeloablative conditioning, using donor-derived anti-3rd party central memory CD8 veto T cells (Tcm). In the present study, we investigated the ability of this relatively safe transplant modality to eliminate autoimmune T-cell clones in the NOD mouse model which spontaneously develop T1DM. Our results demonstrate that using this approach, marked durable chimerism is attained, without any transplant-related mortality, and with a very high rate of diabetes prevention. TCR sequencing of transplanted mice showed profound changes in the T-cell repertoire and decrease in the prevalence of specific autoimmune T-cell clones directed against pancreatic antigens. This approach could be considered as strategy to treat people destined to develop T1DM but with residual beta cell function, or as a platform for prevention of beta cell destruction after transplantation of allogenic beta cells.

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Proton Beam Radiotherapy for Refractory Bilateral Retinoblastoma in Israel

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Background: External beam radiotherapy (EBRT) is a well-established treatment modality for various pediatric malignant tumors; however, its utilization in children with Retinoblastoma, especially those harboring the Rb1 germline mutation, poses challenges due to the several long term effects, mainly, the heightened risk of secondary malignancies. Proton beam therapy (PBT) offers a promising alternative, delivering therapeutic doses with minimal impact on surrounding tissues. Until recently, PBT was accessible only outside Israel, necessitating families to seek treatment abroad for extended periods. We present the inaugural case of PBT administered to a toddler with resistant bilateral Retinoblastoma within the country.

Results: A 4-month-old infant diagnosed with bilateral Retinoblastoma (groups A/E) and a Rb1 germline mutation, devoid of familial history, underwent three cycles of chemotherapy resulting in a complete response in the left eye, albeit with vision loss. The right eye exhibited persistent tumor recurrences near the optic nerve head despite various interventions. At the age of 4 years, facing the threat of blindness and as a final recourse prior to enucleation, the patient received PBT (P-Cure, Shilat Industrial Zone) without sedation. The oncological response was complete, and no side effects were observed. This marks the pioneering instance of pediatric PBT treatment within Israel.

Conclusions: The administration of PBT for refractory bilateral Retinoblastoma in Israel proves both effective and safe. This milestone underscores the feasibility and success of PBT as a local treatment option, offering a viable solution to mitigate the risks associated with conventional EBRT.

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Session II – HEMATOLOGY

HHV6 Triggered Hemophagocytic Lymphohistiocytosis a Multi-Center 7-Case Series

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HHV6 is not considered a common cause of hemophagocytic lymphohistiocytosis. We aim to describe the clinical manifestation of this rare phenomenon in a group of children.

Data retrospectively evaluated from Children's Minnesota (US) showed that 5/52 (9.6%) patients with HHV6 infection had HHV6 induced HLH. Additional two children from Meir Medical Center were diagnosed with HHV6-HLH. All patients had PCR confirmed HHV6. Median age 1.75 years and 71% <3 years. Six patients had ≥ 5 of 8 HLH-2004 criteria, whereas the one with 4/8 had high ferritin, high IL2R level, elevated activated T-cells and severe liver dysfunction. Hemophagocytosis was noted in all 5 of the patients evaluated with a bone marrow biopsy. All 7 patients had thrombocytopenia, elevated IL2R, and liver dysfunction. Notably 4 had seizures and 2 had encephalopathy for a total of 6/7 (86%) considered CNS positive. Associated conditions were DRESS 2nd to carbamazepine (Tegretol) in one patient and Kabuki syndrome (MLL2 heterozygote) with IgG deficiency in another. In 5 patients gene panel for HLH was negative, but subsequent whole exome panel revealed *TNFRSF13B* heterozygote mutation in one patient. Therapy included HLH-2004 to 4/ (57%) patients, IVIG + dexamethasone to one patient and methylprednisolone to one patient. The DRESS patients recovered after carbamazepine discontinuation. All have completely recovered with no HLH recurrence at a median of 5.9 years, and except for the Kabuki-associated IgG deficiency all have no noticeable immune deficiency.

In conclusion, almost 10% of children with HHV6 positive PCR can develop HLH, with significant CNS involvement. The outcome of this group of patients was excellent with no HLH recurrence at a long follow up. The finding of *TNFRSF13B* mutation only by full exome suggests that full exome should be considered in HHV6-HLH patients.

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Compassionate use of Emapalumab in Children with Life-Threatening Disorders_ Real World Data

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Introduction: Life threatening hyperinflammation occurs in hemophagocytic lymphohistiocytosis (HLH) and during acute rejection of hematopoietic stem cell (HSC) grafts. Emapalumab, a monoclonal antibody binding IFNγ, is approved by the FDA for refractory or recurrent primary HLH (pHLH) or in patients intolerant to conventional therapy. Off-label use of emapalumab has been reported for treatment of secondary HLH (sHLH) and for HSC graft rejection. Pending Israeli Ministry of Health approval of emapalumab for clinical use, emapalumab is available in Israel exclusively though compassionate care from Sobi Pharmacutics. Experience that accumulates through on- and off-label use of emapalumab enriches the knowledge base regarding the uses of this drug in the real-world clinical setting.
Methods: We summarized the data of patients receiving emapalumab at our tertiary pediatric center. The medication was received after application to the MAP sponsored by Sobi International with import approval of the Israel Ministry of Health on a named-patient basis.
Results: Nine patients (Pt) aged 2.5 months-17.5 years were treated with emapalumab between 3/2020-3/2024. Patients 1-5 fulfilled HLH-2004 diagnostic criteria. Indications for the use of emapalumab included treatment of HLH in a newborn with severe hepatotoxicity after etoposide (Pt. 3), treatment of acute graft rejection (Pt.1, 6-9), recurrent pHLH after late HSC graft failure (Pt. 4), sHLH with multi-organ failure (MOF) requiring extracorporeal membrane oxygenation (ECMO) (Pts 2&5) and suspected primary and/or 2nd acute graft rejection after HSCT(Pts.6-9). The patient- outcomes were closely related to their clinical status at treatment initiation. Pts. 3&4 were able to reach remission and successfully bridge to SCT. Pt. 1 expired after initial graft failure, severe sepsis and relapsed pHLH. Pts. 2&5, despite showing improvement of their HLH criteria after treatment with emapalumab, succumbed to MOF. Pts. 6-8 underwent successful 2nd HSC transplants with early emapalumab treatment for suspected re-rejection. Pt. 9 underwent a haploidentical transplant for severe acquired aplastic anemia, received emapalumab with dexamethasone for suspected acute rejection and then engrafted.
Conclusions: Emapalumab is a safe, effective, and well tolerated treatment for various HLH or similar hyper-inflammatory scenarios. Administration of emapalumab early in the disease course is likely to be more effective as compared to administration of the drug when MOF has occurred or when HSC graft rejected has occurred. Since these diseases are life-threatening, availability of emapalumab is essential to expedite treatment before irreversible organ failure ensues.

Thursday, May 2, 2024 (cont.)

Session III – ONCOLOGY

Identifying Cell Free DNA in Cerebrospinal Fluid of children with Brain Tumors - A Powerful Tool for a Rapid and Less Invasive Diagnosis and Follow Up

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Background: Whole-genome nanopore sequencing (WGNS) is a third-generation sequencing technology that provides the possibility of methylation analysis of cell free DNA (cfDNA). We aimed to evaluate the feasibility of usage of this technology for liquid biopsies (LB) in the Cerebrospinal Fluid (CSF) of children with Brain tumors and suspected extraocular Retinoblasoma (EORB).
Methods: Samples were collected in several time point before and during treatment course from 3 patients with EORB, in one case of Pinealobalstoma and a child with presumed unresectable spinal cord mass. WGNS was employed to identify methylation profiles of cfDNA. Results of tumor cfDNA in CSF were compared to established cancer databases.
Results: In all 3 cases of EORB cfDNA was negative when imaging studies and CSF cytology were also negative. Contrastingly, in a patient with Pinealoblastoma, and n 2 events in a CNS EORB patient, cfDNA was positive when tumor was evident by MRIs and biopsies. It turned negatve after treatment commenced and remained so. In the patient with the spinal cord mass cfDNA methaltion was consistent with glioblastoma, IDH wildtype, subclass MYCN. A biopsy that was done later in a different hospital was consistent with that diagnosis.
Discussion: These preliminary results represent a new application of cfDNA in CSF using methylation profiles to identify and follow responses of certain CNS tumors. This breakthrough offers hope for a quicker and less invasive diagnostic procedure, and also better monitoring of treatment response, in brain tumors.

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The importance of PET-CT Timing in the Identification of Lymph Node Involvement in Osteosarcoma

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Aims: To evaluate the importance of PET-CT timing in the identification of lymph node involvement in osteosarcoma
Methods: We reviewed the medical records and PET-CT exams from all patients treated for osteosarcoma in our pediatric haemato-oncology department between January 2017 and December 2023.
Results: All patients had PET-CT prior to chemotherapy initiation to evaluate disease extent. In 47 patients, PET-CT was conducted after biopsy, while in 5 patients it was performed before biopsy. 36 of 47 patients had enlarged lymph nodes on post biopsy PET-CT. Among them, radiologists defined 9/36 patients as suspected lymph nodes disease involvement, according to FDG uptake intensity and 7/9 had lymph node dissection, all of which were negative for disease involvement. In 15/36 patients, the interpretation indicated differential diagnosis between post- biopsy reactive lymph nodes and disease involvement, most of them were not biopsied 12/36 cases were defined as reactive lymph nodes based on radiological findings.
In 4 out of the 5 patients that underwent pre biopsy PET-CT no lymph node enlargement was demonstrated. The only patient with lymphadenopathy was diagnosed with lymph node metastatic disease by biopsy.
Conclusion: Performing PET-CT prior to biopsy, as done in 5 cases in our cohort, may prevent unnecessary procedures and lower the risk of underdiagnosis of lymph node involvement in cases where PET-CT are inconclusive.

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Gastric Burkitt Lymphoma- Case Series and Review of the Literature

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Background: Burkitt lymphoma ranks as the third most prevalent cancer among pediatric patients below 15 years old, following acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma (HD). It stands as the predominant subtype of non-Hodgkin lymphoma in the United States. Burkitt tumors predominantly manifest in the lymph nodes (56%), abdomen (21%, primarily affecting the small or large intestine), and bone marrow (14%, also termed Burkitt cell leukemia).
Primary gastric Burkitt lymphoma is rare, with only a few case reports and small case series documenting its occurrence. During prephase chemotherapy, management should consider the potential risk of gastric perforation.
Methods: We conducted a retrospective data collection encompassing all pediatric oncology wards across Israel. Our aim was to document every instance of gastric Burkitt lymphoma over the last two decades. This comprehensive review included details such as age at onset, presenting symptoms, treatment modalities employed, and the corresponding responses to these treatments.
Results: We encountered seven cases characterized by primary gastric Burkitt lymphoma, all of which were male patients. Disease stage was 2-3. Five patients were treated with LMB 2009 (SR) protocol and two patients received protocol Inter-B-NHL ritux 2010. Unfortunately, one patient succumbed after an extended treatment course involving several lines of therapy due to refractory disease. There were no instances of documented gastric perforation. Gastroscopy was not universally performed across all cases, and the status of H. pylori and EBV infections was inconsistently documented.
Discussion: Primary gastric Burkitt lymphoma represents a rare occurrence, with scant information available regarding optimal management and the prevention of gastric perforation during pre-phase chemotherapy. Drawing from our experience with a limited number of cases, the prognosis appears to align with what is reported in medical literature. Our aim is to stimulate collaboration and data-sharing among different countries to enhance our understanding of disease presentation, preventive strategies, treatment outcomes, and suitable follow-up protocols.

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Session V – ONCOLOGY

Neuroblastoma-Specific Clinically Validated Liquid Biopsy Panel Improves Detection of Targetable Variants

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Despite breakthroughs in precision oncology, patients with pediatric solid tumors have seen minimal improvement in outcomes. Development of targeted therapies has yet to significantly impact pediatric oncology, where tumors harbor a paucity of mutations at diagnosis, and difficulties in tissue sampling have limited study of clonal evolution. Pediatric solid tumors demonstrate spatial and temporal intra-tumor genetic heterogeneity, and relapsed tumors, nearly uniformly fatal, are enriched for clinically actionable mutations often present sub-clonally at diagnosis. Non-invasive serial liquid biopsy has the potential to overcome these challenges; however, commercially developed liquid biopsy panels are optimized for adult malignancies and have limited utility in pediatric oncology. To address these challenges, we developed a neuroblastoma specific targeted liquid biopsy panel. We performed comprehensive neuroblastoma literature and genomic dataset review and selected 23 genes that are recurrently mutated and potentially targetable. We collaborated with ArcherDX to design a sequencing panel to target coding regions of these genes and optimize detection of clinically significant copy number aberrations including MYCN, ALK, and ATRX. We validated panel performance to a limit of detection of 0.1% variant allele frequency with minimal 30 ng of input material. Our panel demonstrated superior performance to commercially available platforms and has undergone CLIA-CAP certification to become available for clinical serial monitoring of all patients with neuroblastoma

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The Power to Heal Ourselves - Promising Results for Users of Serum Eye Drops

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Blood-derived autologous/allogeneic serum eye drops are an important treatment for severe dry eye disease. Patients who suffer from severe dry eyes due to their illness, for example: GVHD or Sjögren's syndrome, can improve their condition and prevent damage to the cornea. Bio iDrops at the Rambam blood bank is a joint service with the ophthalmology department whose purpose is to produce these special eye drops while utilizing the knowledge and experience of the blood bank laboratory in the donation, production preparation and documentation of various blood components and in accordance with the accepted protocols.

Aim: to assess the treatment satisfaction among our ocular surface disease patients treated with autologous/allogeneic serum eye drops.
Methods: during 2023, 683 preparations were made for 418 patients. Patients were asked to fill out a dedicated questionnaire: OSDI - Ocular Surface Disease Index in which they rated the severity of their condition before and after a round of 3 months of serum treatment. in addition to these 418 adult patients, 8 pediatric patients (age 3-17) where also treated with serum eye drops, 3 with autolougus serum and 5 with allogeneic serum donatad by a healthy blood donor. All suffered from severs dry eye, 5/8 due to GVHD.
Results: Out of 88 patients who filled out questionnaires as required, 88% rated their pre-treatment condition as suffering from severe dry eye, 8% as suffering from moderate dry eye and 5% as suffering from mild dry eye. After 3 months of treatment only 40% defined their condition as suffering from severe dry eye (a decrease of 45% $p<0.001$), 20% as suffering from moderate dry eye and 20% as mild dry eye with 19% defined as normal (resolution of dry eye disease) (Fig.1).
Conclusions: serum eye drops preparation service at the hospital's blood bank increases the availability of the unique and successful treatment as well as enables multidisciplinary treatment in collaboration with hematologists, specialist ophthalmologists and blood bank laboratory workers. Allogeneic preperations enable young children to benefit from this effective treatment as well.

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Veno-Occlusive Disease in Pediatric Patients Following Hematopoietic Stem Cell Transplantation: Prognostic Factors Associated with Mortality

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Background: Hepatic Veno-occlusive disease is a life-threatening complication of HSCT that belongs to a group of diseases increasingly identified as transplant-related, systemic endothelial diseases. Severe VOD results in multi-organ dysfunction with high mortality rate.
Methods: A retrospective cohort study including 1243 children with malignant and non-malignant diseases that underwent HSCT in two large pediatric hospitals over 20 years. One hundred and one patients (8.1%) developed VOD post HSCT. The objective of the study was to evaluate the incidence and characteristics of VOD and analyze the outcome and risk factors for mortality.
Results: Most patients developed VOD post Allogeneic HSCT (76.2%) versus Autologous (23.8%). The incidence of VOD was twice as frequent in children with malignant diseases compared to non-malignant (68.3% vs 31.7%). A much higher incidence of VOD occurred in patients after Busulpan-based regimen versus TBI-based and Treosulfan-based, 72.3%, 17.8% and 1% respectively. The overall survival of the whole group was 50.5%. The One-hundred-day survival rate of HSCT patients with VOD complication was 81.8%. Mortality predictors included previous infections before transplant ($p=0.013$), conditioning regimen ($p=0.01$), abnormal liver function ($p=0.019$), presence of ascites ($p=0.019$) and need for PICU hospitalization ($p<0.01$) as characteristics of severity of VOD. There was not a significant difference in survival rate between two treatment groups.
Conclusion: Severe VOD in pediatric patients following HSCT still remained life-threatening complication with high rate of mortality. Early diagnosis and treatment with Defibrotide is critical for management of this complication. The addition of steroids to Defibrotide in treatment of VOD does not improve the outcome of children with VOD.

Friday, May 3, 2024 (cont.)

Session VII – HEMATOLOGY/BMT

POSTER PRESENTATION

Symptomatic Corpus Luteam Hemorrhage in Adolescent Females with ITP

Alexander Yelak[1], Anat From[2], Oded Gilad[1,3], Dafna Brik Simon[1], Shiri Rubin[3], Miriam Cohen[1], Carina Levin[4,5], Doua Bakry[6], Shai Izraeli[1,3], Hannah Tamary[1,3], Joanne Yacobovich[1,3], Orna Steinberg-Shemer[1,3,7]

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Immune thrombocytopenia (ITP) is the most common acquired bleeding disorder in children. ITP usually present with minor mucocutaneous bleeding, and only some have severe hemorrhage at presentation or during the course of the disease. Corpus luteum hemorrhage (CLH) is usually asymptomatic but may lead to severe intraperitoneal bleeding in patients with coagulation disorders. Most adult females described with symptomatic CLH had coagulation factor deficiencies or were under anticoagulation treatment, and the minority had thrombocytopenia. In the adolescent female population, CLH leading to intraperitoneal bleeding is rare; only three cases of adolescent females with ITP and intraperitoneal bleeding resulting from CLH were previously described.

This paper aims to shed light on the potential role of ITP as a risk factor for symptomatic CLH. We present three adolescent females with ITP that had CLH and intraperitoneal bleeding; two presented with CLH at the time of ITP diagnosis and the third had chronic ITP. The clinical presentation was similar in all cases including an acute onset of abdominal pain. All three had platelet counts below 20 x109/L at the time of bleeding and dropped hemoglobin levels to below 7.5 g/dL, requiring blood transfusion. All three patients received treatment with intravenous immunoglobulin and steroids and 2 were also treated with tranexamic acid and hormonal therapy. All three patients had normal coagulation functions, excluding disseminated intravascular coagulation as a contribution to the bleeding manifestations or thrombocytopenia. Additionally, none of the patients had documented treatment with NSAIDs prior to their presentation.

Based on the occurrence of symptomatic CLH among adolescent female patients with ITP in our center, we suggest that CLH may be considered a severe complication of ITP, requiring a strong index of suspicion to direct therapy. Larger studies are needed to estimate the accurate prevalence of this complication among adolescent female patients with ITP.

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Epigenetic Liquid Biopsy Reveals Turnover Dynamics of Erythroid Cells Expressing Fetal Gobin in Sickle Cell Disease

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The postnatal switch in globin gene expression is associated with methylation of the fetal (gamma) globin gene and demethylation of the adult (beta) globin gene. In patients with sickle cell disease (SCD), spontaneous or drug-induced expression of the gamma globin gene, or alternatively expansion of erythroid progenitor cells that express fetal globin (F-cells) may compensate for defective beta globin and cause clinical remission. Monitoring the underlying DNA methylation dynamics in this process in vivo has been challenging since erythrocytes accessible in systemic circulation are enucleated. Here we study methylation patterns of circulating cell-free DNA (cfDNA) fragments to assess fetal globin methylation in vivo. cfDNA from premature babies, but not healthy adults, contains demethylated fragments of the gamma globin gene. The cfDNA of patients with SCD or thalassemia contains elevated levels of demethylated gamma globin compared with healthy adults, revealing increased turnover of F-cells. SCD patients have a higher frequency of demethylated gamma globin DNA in their erythroblasts, seen as a higher ratio of demethylated gamma to other erythroblast markers in cfDNA. Monitoring fetal globin methylation in cfDNA provides a non-invasive means to study epigenetic regulation of the globin gene in sickle cell patients and its therapeutic modulation.

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Presence of "ACKR1/DARC Null" Polymorphism in Arabs from Jisr az-Zarqa with Benign Ethnic Neutropenia

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Neutropenia is a reduction in circulating polymorphonuclear cells, with an absolute neutrophil count (ANC) < 1.5 × 109. Benign ethnic neutropenia (BEN) is the most common form worldwide, characterized by an ANC ranging from <1.5 × 109 to <2.5 × 109, and it does not predispose to infections. BEN is observed in various ethnic groups, including Arabs and Yemenite Jews. The inheritance pattern of BEN remains complex, in Sudanese or Arabic origin an autosomal dominant or codominant manner is suggested, while in people of African descent an autosomal recessive inheritance pattern is associated with the null Duffy genotype. The Duffy blood group chemokine receptor gene (DARC/ACKR1) on chromosome 1q22.23, specifically the -67T>C-5 prime UTR (rs2814778) polymorphism in the putative GATA binding site, leads to a nonfunctional allele. While the Duffy antigen is present in the wild-type (T/T) and heterozygous (T/C) phenotypes, it is absent in the homozygous state (C/C), referred to as the ACKR1-null allele. This plays a role in BEN, affecting inflammation, susceptibility to malaria, and cancer complexities (including triggering cell senescence, suppressing metastasis, and increasing likelihood of neutropenic fever following chemotherapy).

Jisr az-Zarqa, an Israeli Arab town on the northern Mediterranean coast, has a 500-years history and an absolute Muslim-Arab population. Founded during the Ottoman era by various families, it is relatively isolated, practicing endogamy, potentially enriching recessive and dominant alleles. While the prevalence of BEN in individuals of Arab descent has been noted, the genetic etiology is yet unexplored. In this study, we determined the presence of BEN and the ACKR1-null allele in a socially closed Arab-Muslim community in Israel.

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Cryogenic Scanning Electron Microscopy Study of Hereditary Hemolytic Anemias

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Background: Hereditary hemolytic anemia is a condition when the red blood cells (RBCs) are destroyed because of genetic mutations. This is a heterogeneous group of genetic disorders that include RBC membrane disorders, RBC enzymatic defects, and hemoglobinopathies, such as sickle-cell disease (SCD) and β-thalassemia. Different disorders may overlap, resulting in a wide range of clinical symptoms. Imaging techniques, especially light microscopy (LM), are essential for diagnosis hemolytic anemias. However, the indication of the unique structural properties of different types of cells and the evolution of their morphological changes upon specific conditions requires high-resolution methods.
Cryogenic scanning electron microscopy (cryo-SEM) combined with high-pressure freezing (HPF) specimen preparation can provide new high-resolution information to hematological research. It allows examination of cell morphology and ultrastructure, interactions between blood components, and cell dynamics with nanometric resolution, close to their native state. Cryo-SEM is still rarely used for the evaluation of blood cells, and the aim of the work was to demonstrate the potential of this technique for hematological research.

Methods: Whole blood samples from the patients with β-thalassemia major, homozygous and heterozygous cases of SCD, and with glutamate-cysteine ligase (GCL) deficiency and β-thalassemia trait coinheritance, were evaluated and compared with a healthy control, S trait person, GCL deficiency heterozygote, and a β-thalassemia carrier controls. The SCD blood samples were incubated with sodium metabisulfite to provide low-oxygen conditions and induce morphological changes. These samples were examined using LM, flow cytometry, and cryo-SEM at different stages of sickling.
Cryo-SEM samples were prepared by high-pressure freezing (HPF). The uncoated cryo-specimens were imaged by a Zeiss Ultra Plus cryo-SEM, equipped with a field emission gun, at low beam acceleration voltage (1.2 kV). No cryoprotectants or stains were used.

Results: Cryo-SEM reveals abnormal morphology in most RBCs from the patients. Blood specimen from a patient with β-thalassemia demonstrates evidence of cytoskeleton rupture with indicative membranal damage. Fig. B demonstrates the shell-like RBC morphology that was the most common in this patient. We followed the changes of erythrocyte morphology in the SCD patients due to the hypoxia condition, when focusing on different stages of the sickling process. Fig. C shows the typical sickled RBC characteristic of SCD patients after exposure to low-oxygen conditions. In the patient with GLC deficiency and β-Thalassemia Trait Coinheritance, we found a variety of RBC morphologies and signs of membranal damage including membranal blebbing and in some cases almost complete cell disintegration (Fig. D). These abnormalities are not seen in RBCs from carriers and healthy individuals (Fig. A).

Conclusions: This work presents the first study of RBC morphology and ultrastructure in patients with hereditary hemolytic anemias using the novel cryo-SEM methodology. The micrographs reveal details of the erythrocytes that cannot be seen using conventional methods. We found membrane and morphological abnormalities that define the hemolytic process in these diseases. We also proposed the mechanism for RBC sickling process in SCD patients. This study highlights the potential of the cryo-SEM methodology for deeper understanding of hematological disorders.

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Hemoglobin City of Hope May Cause Severe Microcytic Anemia When Co-inherited with an Additional Variant in Beta-Globin

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b-thalassemia encompasses a spectrum of disorders varying from isolated microcytosis, through non-transfusion-dependent thalassemia (NTDT) to transfusion-dependent thalassemia. Hemoglobin City-of-Hope (Hb-COH) involves a substitution of glycine to serine in position 69 of b-globin (HBB:c.208G>A ,p.Gly69Ser). Very few patients carrying the Hb-COH variant were described so far. Heterozygous individuals were reported as asymptomatic. Three patients were reported with compound heterozygosity for Hb-COH and a pathogenic variant in b-globin and presented with a spectrum of severity ranging from isolated microcytosis to NTDT. No patients were described with homozygosity for Hb-COH. Therefore, information is lacking for genetic counseling regarding the clinical implication of inheritance of this variant. Thus, we aimed to analyze the phenotype-genotype correlation in patients possessing the Hb-COH variant.

We present 31 patients diagnosed with Hb-COH between 2000-2022 at the Schneider Children's Medical Center and at the Hadassah Medical Center. Seven patients were compound heterozygous for Hb-COH and a pathogenic variant in b-globin. All these patients had markedly microcytic anemia with mean Hb levels of 8.6 g/dl (SD 0.77) and mean corpuscular volume (MCV) levels of 57.5 fl (SD 5.6). All patients had normal iron stores. The most severe patient co-inherited Hb-COH with the c.92+5G>C variant of b-globin and had hemoglobin levels below 8g/dl, but did not require blood transfusions. Three patients were homozygous for the Hb-COH variant; both had low levels of Hb for age with normal iron stores. Fourteen patients were heterozygous for Hb-COH. All had normal hemoglobin levels for age (mean 12.8 g/dl, SD 1.5) and MCV levels (mean 85.6 fl, SD 7.4). Seven patients co-inherited Hb-COH with the common -α3.7 deletion and also had normal levels of Hb and MCV.

To conclude, Hb-COH is a rare variant in the b-globin gene, which is asymptomatic in the carrier state, thus considered "silent". When co-inherited with an additional pathogenic variant in b-globin, patients may present with NTDT. We show, for the first time, that homozygosity for this variant may cause mild anemia, however, larger cohorts are required for definite conclusions. Understanding how this variant correlates with the phenotype is important for clinical management and for genetic counseling.

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Risk and Promise: An 11-Year, Single-Center Retrospective Study of Severe Acute GVHD in Pediatric Patients Undergoing Allogeneic HSCT for Nonmalignant Diseases

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Background: Hematopoietic stem cell transplantation (HSCT) is the only curative option for many nonmalignant hematopoietic-derived diseases in pediatric patients. Survival after HSCT has improved in recent years and resulted in a 90% survival rate and cure in some nonmalignant diseases. Graft-vs.-host disease (GVHD) remains a frequent and major complication of HSCT, and a leading cause of morbidity and mortality. Prognosis of patients with high-grade GVHD is dismal, with survival rates varying from 25% in the adult population to 55% in pediatric patients.

Methods: The main aim of this study is to evaluate the incidence, risk factors, and outcome of severe acute GVHD (AGVHD) in pediatric patients with nonmalignant diseases, following allogeneic HSCT. Clinical and transplant data were retrospectively collected for all pediatric patients who underwent allogeneic HSCT for nonmalignant diseases at the Hadassah Medical Center between 2008 and 2019. Patients who developed severe AGVHD were compared with those who did not.

Results: A total of 247 childrenwith nonmalignant diseases underwent 266 allogeneic HSCTs at Hadassah University Hospital over an 11-year period. Seventy-two patients (29.1%) developed AGVHD, 35 of them (14.1%) severe AGVHD (grade 3–4).

Significant risk factors for developing severe AGVHD were unrelated donor ($p < 0.001$), mismatch donor ($p < 0.001$), and the use of peripheral blood stem cells (PBSCs) ($p < 0.001$). Survival rates of pediatric patients with severe AGVHD was 71.4%, compared with 91.9% among those with mild (grade 1–2) AGVHD and 83.4% among patients without AGVHD ($p=0.067$).

Conclusions: These results demonstrate a high survival rate in pediatric patients with nonmalignant diseases despite severe GVHD. Significant mortality risk factors found in these patients were the source of donor PBSC ($p = 0.016$) and poor response to steroid treatment ($p = 0.007$).