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ABSTRACT BOOK

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Background: The detection of extremely small clone (<0.01%) became possible through high-sensitive flow cytometry (FCM), but the clinical significance of small PNH clone has not been elucidated.
Aims: To investigate a correlation of *PIGA* mutation and small PNH FCM clone, we measured PNH FCM clone size and mutant burden of *PIG* gene, with their correlation to treatment response.
Methods: A total of 89 specimens from 63 patients whose PNH clone size was ≥0.1% by FCM was enrolled (classic PNH 9, PNH related with bone marrow disorder 47, subclinical PNH 10). To detect minor cell population with *PIG* mutation, we adopted ultra-deep sequencing for *PIGA, PIGM, PIGX and PIGT* mutation.
Results: Twenty two% of 63 patients with PNH FCM clone harbored *PIG* gene mutation and 92.8% of patients with *PIG* mutation had >10% PNH FCM clone in RBC and granulocyte. In classic PNH patients (n=6), the average of PNH FCM clone size was 56.8% in RBC and 89.6% in granulocyte, and all patients had *PIG* gene mutation. In patients with subclinical PNH clone, the average of PNH FCM clone was 1.8% in RBC and 3.3% in granulocyte, while *PIG* gene mutation was not detected. In the patients with coexisting bone marrow disorder (BMD), the average of PNH FCM clone size was 8.0% in RBC and 14.9% in granulocyte. Among 6 patients with Eculizumab treatment, hemoglobin increment and decrease of FCM RBC clone size correlated, while LDH decreased in all patients, irrespective of treatment response. Decrease of the ratio over 0.15 (type III/type II+III PNH clone in RBC) was a predictive factor for complete response at 6 months from treatment initiation. Of the 11 patients with consecutive results of *PIG* mutation, 88% of patients with *PIG* mutations was non-responsive to supportive treatment, while 33% of patients without *PIG* mutations was non-response (p=0.072). Mutant burden of *PIG* gene mutation were not changed during treatment irrespective of types of treatment.
Summary/Conclusion: The *PIG* gene mutation was detected only in patients with >10% FCM PNH clone and The mutation burden of *PIG* gene was related to the granulocyte FCM PNH clone size. The presence of *PIG* gene mutations was correlated with adverse treatment response. We suggest monitoring of PNH clone in RBC can be a potential predictor of treatment response as well as Hb during treatment with Eculizumab.

PB1833

CLINICOHEMATOLOGICAL AND CYTOGENETIC PROFILE OF APLASTIC ANEMIA IN PAKISTAN

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Background: Aplastic anemia are acquired or congenital anemias associated with hypocellular bone marrow. The exact etiology is unknown but several factors are considered to be causative for suppression of hematopoitic cell production resulting in aplastic anemia.
Aims: This entity considered to be uncommon is frequently prevalent with rising trend seen especially in Pakistan. This is quite contrast to what is observed in west. Moreover, there is scarce local data. Hence the study was done to assess baseline clinical and cytogenetics features of patients presenting with aplastic anemia.
Methods: This study was approved by the Institutional Ethics Committee of National Institute of Blood Diseases and Bone Marrow Transplantation. In this cross sectional study,122 patients with aplastic anemia were enrolled during the period of June 2016 to January 2018. Informed consent was obtained prior to the study. Data collected included demographic information, laboratory information, includinggender, symptoms, treatments, blood counts and chemistry parameters including urea, creatinine and liver function tests.Viral profile included Anti-HCV, Anti-HBsAg, HIV I/II and Cytomegalovirus (CMV) performed. Cytogenetic analysis was performed on bone marrow samples and karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN) 2013, karyogram were made using Meta system. Variables were evaluated using SPSS version 23.
Results: A total of 122 patients were included in the study. The median age of the patients was 14±12.59. A slight predominance of males were observed which were (n=76, 62%). Fever and weakness were the most complain found in (n=56, 46%) followed by colitis (n=24, 20%), gum bleeding (n=20, 16%) bruises (n=12, 10%) and shortness of breath in (n=10, 8%) patients. All patients were grouped according to camitta classification. Non severe aplastic anemia were observed in (n=100, 82%) followed by very severe aplastic anemia (n=12, 10%) and severe aplastic anemia (n=10, 8%). The mean hemoglobin was 7.61±2.11g/dl, red blood cells 3.17±3.4x10^{12}/l, MCV 89.2±11.56fl, total leucocytes counts (tlc) 3.09±2.03x10^{9}/l, absolute neutrophils count 0.7±0.99×10^{9}/l and platelets counts were 27±52.29x10^{9}/l. The mean total bilirubin was 0.76±0.38mg/dl, direct bilirubin 0.37±0.27mg/dl, alanine aminotransferase (SGPT) 61±89.5u/l and alkaline phosphatase was 201±116.5u/l. Out of 122 patients, chromosomal breakage was observed in (n=10, 8%) patients. Anti HbsAg was positive in (n=04, 3%) and anti HCV in (n=02, 1.6%).CMV was positive in (n=02, 1.6%) patients.
Summary/Conclusion: In our study we have observed lower median age andmale predominance.Non severe aplastic anemia was most common. Raised SGPT was seen in many indicating liver damage. To overcome adverse prognostic implications, early identification of such patients with close clinical follow up and upfront stem cell transplant must be considered. This study was done retrospectively yet represents a large cohort of aplastic anemia in the country. In future, prospective studies are needed to be done to elaborate disease biology and clinical outcome of the baseline adverse disease characteristics observed in our study.

PB1834

ADA 2 ENZYME DEFICIENCY MANIFESTING AS PURE RED CELL APLASIA

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Background: Pure red cell anemia is characterized by normochrome normocytic anemia with severe reticulocytopenia and marked decrease or absence in red cell lineage in bone marrow. We herein present a child with congenital pure red cell anemia diagnosed as ADA2 enzyme deficiency to emphasize this rare etiology of pure red cell anemia.
Aims: A 40 day old boy was admitted to our hospital with pallor. On physical examination, there was no hepatosplenomegaly or any stigmates. His laboratory work up showed severe anemia, hgb:2 gr/dl; htc:%5.8; wbc: 9750/mm^3; neu: 1800/mm^3; plt: 690 000/mm^3; MCV:89 fL; LDH:360 U/L. Electrolytes, kidney function tests, and liver function tests were normal. Direct coombs test was negative, reticulocyte count was low (0.2%). On blood smear, erythrocytes were normal in shape and size with no signs of hemolysis. On follow up he was transfusion dependant monthly. Bone marrow aspiration showed decreased erythrocyte progenitor cells. HbF was 5.8%. Viral serology including Parvovirus was negative. Vitamin B12 and folate levels were normal, erythropoetin was 39.9 mU/ml (increased). The diagnosis of pure red cell aplasia was established. He also had a history of recurrent infections and his immunoglobulins were low. The genetic analysis for DBA was negative.
Methods: Whole exome sequencing, showed CECR1 mutation causing ADA-2 enzyme deficiency. His parents were silent carriers. The patient's follow up continues in our outpatient clinic, he receives erythrocte tranfusion and intravenous human immunglobulin monthly.
Results: CECR1 gene is responsible for the synthesis of ADA 2 enzyme which is the major extracellular adenosine deaminase and functions as a growth factor. It was first identified in 2014 in patients with poliarteritis nodosa by exome sequencing and is responsible for a spectrum of autoinflammatory symptoms from vasculitis to thromboembolic events. ADA- 2 enzyme deficiency has been described in around 100 patients until now. Most of the patients had inflammatory symptoms like vasculopathy, lacunar strokes, hepatosplenomegaly or livedo reticularis. Hematologic manifestations were poorly described and unexpected without the inflammatory symptoms or immunodeficiency. In 2016, 5 patients from Israel were reported with hematological manifestations, 2 siblings had congenital pure red cell anemia without any vasculopathy.
Summary/Conclusion: Together with other case reports, our patient represents a new phenotype of this mutation and causes the need for evaluating the functions of ADA 2 in bone marrow.

PB1835

BREAKTHROUGH HEMOLYSIS AND THROMBOEMBOLISM CONTROLLED BY ECULIZUMAB DURING PREGNANCY IN PAROXYSMAL NOCTURAL HEMOGLOBINURIA (PNH): A SINGLE INSTITUTION EXPERIENCE

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Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal stem cell disorder characterized by intravascular hemolysis, cytopenia and thrombophilia. Thromboembolism, infection and premature birth are main reasons for significantly increased maternal and fetal morbidity and mortality during pregnancy and the following post-partum period in PNH patients. Therefore, PNH has been considered a relative contraindication for pregnancy. The terminal complement cascade inhibitor Eculizumab prevents fatal complications and nearly normalizes overall survival in PNH. Consequently, it has become the standard treatment in patients with symptomatic PNH. However, there are limited published data regarding the use of Eculizumab during pregnancy, the postpartum period or, more less, during lactation.
Aims: To evaluate the management of pregnancy in PNH in our institution.
Methods: We report three cases of pregnancy in PNH.
Results: A 28 year old PNH patient became pregnant while on Eculizumab and the therapy was continued throughout the whole pregnancy. At diagnosis of her pregnancy (6th week of gestation) anticoagulation therapy with low molecular weight heparin was initiated and continued although no clinical sign of thrombosis was present. She was immediately introduced in an interdisciplinary team for high risk pregnancies consisting of specialists for gynecology, internal medicine, anesthesia and hematology. During the third trimester she developed a breakthrough hemolysis in terms of symptomatic anemia requiring repeated blood transfusions. Hemolysis was successfully controlled by dose escalation of Eculizumab first from 900mg to 1200mg biweekly and consequently shortening the administration interval from a biweekly to a weekly scheme until the birth of the baby. She successfully delivered a healthy baby at term by natural birth without complications. One month after delivery the patient has returned to her usual therapeutic Eculizumab regimen (900mg biweekly). She breastfeed her baby for six months without complications. The anticoagulation treatment was continued, as recommended, for the first three months. The baby girl is developing well according to her age and she is now one years old. Currently, we are managing other two young pregnant PNH patients. Our second patients is a 27 years old girl who became pregnant while she was not on Eculizumab but only in follow up due to indolent disease without hemolysis. She was started with anticoagulation prophylaxis with low molecular weight heparin as soon as the pregnancy was noted, and she started the standard therapeutic Eculizumab regimen (900mg biweekly) from the beginning of second trimester. She is now at the end of the third trimester, fetal growth is regular, no signs of hemolysis on the mother and no thromboembolic complications were noted. The estimated date of delivery is scheduled for the end of March, 2018. The third pregnancy is on a 27 years old PNH patient currently at the 15th week of gestation; she was on Eculizumab standard regimen treatment from 2009 due to breakthrough hemolysis and we are managing her pregnancy according to the policies followed for the first described case.
Summary/Conclusion: Our single center experience reports a favorable outcome of a PNH patient who became pregnant while under Eculizumab, supporting the scarce published experience that this drug can be given safely and can even be escalated during pregnancy in PNH patients, with a good disease control. We are currently managing other two pregnant PNH patients, at the moment without complications.

PB1836

A CASE OF SEVERE CONGENITAL NEUTROPENIA CARRYING A NOVEL HOMOZYGOUS MUTATION IN CSF3R GENE

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Background: Severe congenital neutropenia (SCN) is characterized by profound neutropenia and a predisposition to life-threatining bacterial infections. Autosomal dominant, autosomal recessive, X-linked and sporadic SCN forms have all been described. Mutations in several genes including ELANE, GFI1, HAX-1, G6PC3 and WAS are responsible for SCN. CSF3R mutations are extremely rare and usually somatic.
Aims: Here we describe an SCN case having a novel homozygous CSF3R mutation.
Methods: A-5-month-old boy was referred to our department because of neutropenia. There was a history of hospitalization because of cervical lymphadenitis and neck abscess at the age of 3 months. The parents were consanguineous. Physical examination was normal (no dysmorphic findings such as leukoplaki, nail dystrophy, brown ridging on the neck, thumb abnormalities, etc.were present). Laboratory tests revealed a severe neutropenia (300/mm^3). Lymphocyte count, serum immunoglobulin levels and peripheral lymhocyte subset analysis were all normal. Viral infection markers were negative. Neutropenia persistedat the level of 200-400/mm^3. In the following8 weekperiod, the neutrophile count was monitored twice weekly. All neutrophile counts were below 500/mm^3. A bone marrow examination revealed normocellularity and maturation arrest of granulocytic series at the level of band form. Cytogenetic studies were normal. The patient did not respond to G-CSF therapy and the neutropenia persisted. The patient is now 21-month-old and has experienced several febrile neutropenia episodes. Bone marrow transplantation has been planned. Unfortunately to date no HLA matched donor within the family has been found.
Results: Molecular genetic analysis for ELA-2, HAX-1, G6PC3, SBDS were normal. However, in the CSF3R genea novel homozygous p.V224D (c.671 (T>A)) mutation was detected. Using in silico analysis this novel mutation was found to be pathogenic. A functional analysis has been planned.
Summary/Conclusion: CSF3R mutations in SCN cases are usually somatic or *de novo* and inherited form is extremely rare (Triot A, *et al.* 2014). It has been considered that the SCN case described here will expand the mutation spectrum of GCSF3R gene and help to make phenotype-genotype correlations.

Rerefence

1. Triot A, Jarvinen PM, Arostegui JI, Murugan D, Kohistani N, Dapena Diaz JL, *et al.* Inherited biallelic CSF3R mutations in severe congenital neutropenia. Blood. 2014 Jun 12;123(24):3811-7.

PB1837

BONE MARROW FINDINGS IN COLLAGEN VASCULAR DISEASES ASSOCIATED WITH CYTOPENIAS

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Background: the collagen vascular diseases area diverse group of inflammatory systemic disorders thought to be immunologically mediatedincluding systemic lupus erythematosus (SLE), scleroderma, polymyositis and polyarteritisnodosa, they are frequently included in the differential diagnosis for unexplained cytopenias and often prompt a bone marrow evaluation in this population is important.
Aims: to study morphologic and immunohistochemical characteristics of bone marrow involvement in patients with collagen vascular diseases associated with cytopenias
Methods: In the current study, we examined 100 patients. The diagnosis of collagen vascular diseases was made according to diagnostic criteria for each as SLICC for SLE.All patients were subjected to thorough history taking, physical examination, and many investigations were done for them including serology (ANA, Anti dsDNA, AntiCCP, RF), and bone marrow examination was done for all patients.
Results: collagen vascular diseases show female predominance regarding SLE and RA with male: female ratio equal 3:14 and 1:4 respectively. Nephritis and arthritis were the most common presentation in SLE and RA respectively and almost present in all patients followed by hematological manifestations as fatigue and ecchymosis. Normocellular bone marrow was the commonest finding in studied patients followed by hypercellular marrow then hypocellular marrow while dysplastic changes affected erythroid element mostly followed by myloid and megakaryocytic elements regarding eosinipgilic, plasma cells and lymphocytic infiltrations; none of them shows statistically significance
Summary/Conclusion: There were no significant statistical differences between CVDs patients as regard bone marrow findingalso there were no specific bone marrow finding detected in SLE and RA patients.

PB1838

A RARE CAUSE OF ANEMIA: GHOSAL TYPE HEMATO-DIAPHYSEAL DYSPLASIA

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Background: Ghosal type hemato-diaphyseal dysplasia (GHDD) is a rare, autosomal recessive disorder characterized by increased bone density with both diaphyseal and metaphyseal involvement and bone marrow dysfunction marked by a corticosteroid responsive, myelopthisic anemia. The gene