GATA 2 Haploinsufficiency in Acute Myeloid Leukemia: Looking Beyond the Obvious

Infections encountered during treatment of leukemias are attributed to neutropenia and chemotherapy-induced immunodeficiency. Genetic disorders that predispose both to malignancies and infections have been recently recognized [1]. We describe a patient with GATA-2 deficiency who was evaluated after a diagnosis of acute myeloid leukemia and repeated infections.

A14-year-old boy presented with progressive anemia, macrocytosis (mean corpuscular volume 102fl), normal leucocyte and platelet count, and peripheral smear suggestive of megaloblastic anemia. He was the only child born to a non-consanguineous couple with no family history of malignancy or severe infections. Clinical examination revealed anemia and growth retardation [height 140 cm and weight 29 kg (both <5th centile)]. There was no fever, lymphadenopathy or hepatosplenomegaly. He was previously well except for episodes of diarrhea which were managed symptomatically. Bone marrow aspiration revealed 31% myeloblasts, which on immunophenotyping were positive for CD13, CD33, CD117, CD34 and negative for T and B lineages. Monosomy 7 was observed in 76% blasts by fluorescent in-situ hybridization. With a diagnosis of high-risk acute myeloid leukemia (AML), he was started on induction therapy (cytarabine, daunorubicin and etoposide). He achieved remission after first cycle following which he received another induction and 3 cycles of cytarabine-based consolidation. He tolerated chemotherapy without any unusual side-effects. Bone marrow transplantation was advised considering high risk AML; however, parents deferred the same.

At initial evaluation for AML, he was noted to have black warts along the hairline of forehead. According to the family the flat warts had been present for the last few years and would shed off occasionally. 6 months after completion of chemotherapy, he started developing episodes of protracted diarrhea. Stool was positive for *Cryptosporidium parvum* which was managed with nitazoxanide. These episodes of diarrhea persisted with weight loss to 25.2 kg. Progressive lymphopenia was noted during this period. Bone marrow and CSF were repeated and continued remission of AML was confirmed. HIV was ruled out. Serum immunoglobulins were normal. Recurrent infections with monosomy 7 associated AML was clinically suggestive of GATA 2 deficiency. Absolute lymphocyte count was done which was 735 cells/μL with 99.8% CD3 cells (733 cells/μL, normal 684-2170 cells/μL).

Next generation sequencing for cancer predisposition genes was performed; a frameshift deletion (chr3: 128205727: TG>T; c.147del) resulting in amino acid change and subsequent termination of the protein, 31 amino acids downstream to codon 49 (p. Phe49LeufsTer31) was detected in the *GATA 2* gene. This is a loss of function mutation which is not reported in ExAC and 1000 genomes databases. The nature of disease and prognosis was explained to parents and bone marrow transplantation was again advised. Upper and lower gastrointestinal endoscopy was done which was normal; thus ruling out mycobacterial infections and colitis which are reported to cause diarrhea. Fourteen months after AML treatment, he developed bilateral lobar consolidation with fatal pulmonary hemorrhage despite aggressive antimicrobial support. CT scan and bronchoalveolar lavage to distinguish between infection and pulmonary alveolar proteinosis although planned, was not performed as the child died within 12 hours of hospitalization.

The GATA (Guanine-Adenine-Thymine-Adenine) family is comprised of six zinc finger transcription factors of which *GATA 2* is vital for the proliferation of hematopoietic stem cells [2]. The gene is located on chromosome 3q21 and >100 heterozygous germline mutations are now known to result in *GATA 2* deficiency or haploinsufficiency. Frameshift or null mutations that abolish *GATA 2* activity tend to present early in life as in our case compared to missense mutations that reduce transcriptional activity [2]. This disorder has protean disease manifestations such as cytopenias (neutropenia, monocytopenia, B and NK lymphopenia, aplastic anemia), myelodysplastic syndrome, acute myeloid leukemia, infections including human papilloma virus, atypical mycobacterial infections and pulmonary alveolar proteinosis [1]. The syndrome complex has been described independently as MonoMAC (monocytopenia

with Mycobacterium Avium Complex), DCML (dendritic cell monocyte and lymphoid deficiency) and Emberger syndrome (sensorineural deafness, congenital lymphedema and viral warts). This is a sporadic entity with autosomal dominant inheritance. Germline *GATA 2* mutations are the most common defect predisposing to pediatric myelodysplastic syndrome with a high prevalence of monosomy 7 thus mandating its evaluation in every case of monosomy 7 associated MDS [3]. Allogeneic hematopoietic stem cell transplantation is the only curative option for both immunodeficiency as well as MDS/AML [4-6].

Evaluating the cause of repeated infections without dismissing them as related to malignancy/chemotherapy has helped us in reaching a diagnosis. Identification of such genetic predisposition not only helps us manage our patients better, but also has implications for donor search for bone marrow transplantation and genetic counseling for the family.

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Acquired Recto-Vaginal Fistula as a Presenting Feature in an Infant with Severe Combined Immunodeficiency

Acquired recto-vaginal fistula in infancy is a rare entity. We report a child with Severe Combined Immunodeficiency (SCID) who presented to us with an acquired recto-vaginal fistula.

A 5½-month-old girl, firstborn of a non-consanguineous marriage presented with constipation for one month and passing stools per vaginum for three days. She was born at full term at our centre, with a birthweight of 3100 grams, to HIV negative parents. Complete physical examination, including the perineum was noted to be normal at birth. She had been hospitalised for culture-negative sepsis without meningitis at day 21 of life and uncomplicated dengue fever at three months of age. She was on exclusive breastfeeding and had received BCG, OPV, DPT, and Hepatitis B vaccines with no reactions. There was no family history of immunodeficiency disorders or unexplained infant deaths. There was no history of trauma, surgery or suspicion of abuse. Her weight was 6.4 kg (0 z score), length was 59 cm (0 to -2 z score). She had a typical BCG scar. Examination of the perineum revealed a fistulous opening next to the vaginal orifice at the nine o'clock position, suggestive of a recto-vaginal fistula and there was no obvious evidence of local infection. Systemic examination was otherwise unremarkable.

Hemogram showed a normal absolute lymphocyte count (ALC) of 7385 cells/cu.mm. She underwent a diversion colostomy, and per-operatively was found to have a fistulous tract extending from the vagina to the rectum by gentle probing. There was no gross evidence of