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The Importance of Family: Recognizing Familial Leukemia A Case and Review of Literature

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Introduction

Familial leukemia is generally thought of as being a rare entity. We recently encountered a patient who had multiple family members treated for acute myelogenous leukemia. Using next generation sequencing we were able to identify a common finding of at least two family members. We suspect this type of penetrance may be more common than first thought.

Case

A 52-year-old female was directly admitted into our hospital by an outside hematologist. Routine blood work prior to hospitalization revealed a relatively normal complete blood count but had the finding of 18% blasts on the peripheral smear. This patient stated that she had been treated in Puerto Rico in her youth for acute myelogenous leukemia. Unfortunately, no treatment records were obtainable as the treatment has been more than 30 years ago. She stated that she received intense chemotherapy but couldn't remember other details. No stem cell transplant was performed. At the time of admission, the patient had blood work done showing a total white blood cell count of 3900 10(3)/ul, hemoglobin 13.4g/dL, and platelet count of 134 X10(3)/ul. 18% blasts were present in the differential. A bone marrow biopsy was done upon admission into the hospital. This biopsy revealed a normocellular bone marrow with background dysplasia and 17% myeloid blasts by flow cytometry. Conventional karyotype and FISH analysis were normal (46 X:X). Next generation sequencing via Neogenomics ® revealed biallelic CEBPA mutations as a sole abnormality. The mutation was biallelic NP_004355.2 with an allele frequency of 51% as a frameshift variant and 15.4% as a protein altering variant. In the patient's family history, she stated she had two daughters who also had a diagnosis of

acute myelogenous leukemia. We were able to get in contact with the transplant physician of one of the two daughters and asked them if testing was ever done on the patient they took to transplant. They were ultimately able to find a report of the daughter they treated having a biallelic CEBPA mutation as well. We were unable to get CEBPA testing of the other daughter at the time this report is written. Much of the care of the patient's family was outside the continental US and further records are unobtainable.

Our patient opted to begin hypomethylation after discussion of both hypomethylation and induction chemotherapy. She is currently responding well and is being typed for an unrelated donor stem cell transplant.

In this review, we will provide an overview of some of the known familial acute myeloid leukemia and myelodysplastic syndrome that have Clinical Laboratory Improvement Amendments (CLIA) certified testing approval. There will a brief discussion regarding each syndrome's genetics, inheritance, prevalence, and management. In choosing to discuss the syndromes with approved testing we would like this paper to serve as a facilitation and reiteration of the importance of screening all patients with AML and MDS to rule out the presences of an underlying familial disorder. Furthermore, there will be a discussion about the patient above and proper screenings methods that could have been implemented to provide counseling and goal directed management to the patient's family members to avoid harm. Although, there are over 100 genes involved in the predisposition to leukemias, this paper will primarily focus on TERC or TERT, familial acute myeloid leukemia AML with mutated CEBPA, familial MDS/AML with mutated GATA2, and familial platelet disorder with propensity to myeloid malignancy.

Familial AML with Mutated CEBPA

CEBPA mutations in AML cases can be sporadic or familial with "the overall prevalence of CEBPA mutations in AML is roughly 10%, [and] up to 1% of cases of sporadic AML could be attributed to Familial AML with CEBPA mutation [1,2]. Both have similar phenotypes and favorable prognosis. But a key difference is the higher rate in which Familial AML develop new future leukemias. This entity is important when dealing with possible familial AML cases especially for family members of the affected.

CEBPA encodes a master hematopoietic transcription factor that acts as a critical regulator of granulocyte and monocyte differentiation [3]. Observation shows that C/EBPα-deficient mice lack mature granulocytes raises the possibility that mutations in the gene encoding C/EBPα (CEBPA) could contribute to the block in differentiation of myeloid progenitor cells in AML [4].

Familial AML with mutated CEBPA is inherited in an autosomal dominant fashion and displays complete or near-complete penetrance for development of AML [5,6,7] meaning almost all patients inheriting the mutated gene go on to develop AML as well as their siblings having a 50% risk of carrying the mutation. Therefore, it's important in distinguishing between the sporadic and familial cases and ensuring they receive the proper management, surveillance

and counseling. This could also have implications in the choice of donor for stem cell transplantation as family members may carry a similar mutation.

The CEBPA mutation, somatic or germline, "confer a relatively favorable prognosis, and CEBPA mutation testing is becoming routine in leukemia diagnosis [8,9]. Its configuring whether the mutation is sporadic or germline that remains so important afterwards. Despite the favorable prognosis, a different approach to management for sporadic and germline should be considered. HSCT remains the definite curative therapy in all cases of AML and therefore those with germline mutations of CEBPA should be offered earlier evaluation due to the higher rate of new leukemia later. Of note, patients with familial CEBPA mutated AML may be at increased risk of developing additional malignant clones after cure of their initial leukemia, often with acquired CEBPA mutations distinctive from those found in the original leukemia [10]. Not only should HSCT be offered earlier, but evaluation of potential donors needs to be more vigilante. Family members usually serve as the best donors for Allo-HSCT because of the high HLA match rate, but because the degree in which CEBPA Familial AML is inherited, those family members must be properly screened and excluded as donors. This serves to delay and lower the efficacy of rate of HSCT and thus needs to be considered per an individual basis.

Because there are no preceding phenotypic abnormalities, diagnosis remains challenging. Family history remains the first alerts to clinicians, so they can order the proper test.

Familial Platelet Disorder with Propensity to Myeloid Malignancy FPD/AML is characterized by platelet dysfunction, often causing clinical bleeding with minor trauma or surgical procedures as well as poor wound healing, mild to moderate thrombocytopenia, and a propensity to develop myeloid malignancies [11]. Due to the numerous different ways the mutation can occur (including but not limited to missense, nonsense, duplications and deletions) had led to variable phenotypic presentations of those who inherited the mutation. These molecular characteristics may account for some of varying risk of leukemia as well [12].

FPD is caused by monoallelic mutations in RUNX1. RUNX1 encodes a sequence-specific transcription factor that is essential for HSC formation in the conceptus and is important for the differentiation of cells of the lymphoid, myeloid, and megakaryocytic lineages [13,14,15,16].

The lifetime risk of MDS/AL in mutation carriers approaches 40%, with an average age of onset of 33 years (range 6-76 years) [17,18,19]. It is critical to properly assess all those affected. What makes difficult to assess is the heterogeneity in which carriers of FPD/AML exhibit in terms of symptoms. This certainly makes a pedigree analysis not as certain.

It is also important to consider that myeloid neoplasms with germline RUNX1 mutations occur with strong anticipation, therefore close follow-ups of the younger members of an affected family are necessary: a baseline blood count with annual checkups, and a bone marrow biopsy in the event of significant changes in the peripheral blood counts [20]. Owing to the fact the underlying mechanism in which leads to RUNX1 causing leukemia remains to be discovered, so much remains in the future in discovery of pathogenesis.

Familial MDS/AML With Mutated GATA2

GATA2 encodes a zinc finger transcription factor critical for normal hematopoiesis [21,22]. Overall the risk of MDS/AML in patients with GATA2 deficiency is estimated at 50% [23]. Compared to patients with primary MDS, patients with GATA2 deficiency tend to be younger and are more likely to have hypocellular MDS [24,23]. The prognosis after MDS/AL development appears to be poor, with the best outcomes reported among those undergoing allogeneic hematopoietic stem cell transplantation [25,26].

Telomere Biology Disorders (TBD) Due to Mutation of TERC or TERT

Heterozygous mutations in the telomerase reverse transcriptase TERT and RNA component–encoding gene TERC may present as familial MDS/AML predisposition syndromes [27]. Those who inherit a single abnormal copy of TERT or TERC have an autosomal dominant TBD with variable clinical manifestations and incomplete penetrance [28,29,30].

Affected individuals within a single pedigree range from those who are completely normal or have only subtle blood count abnormalities such as an elevated MCV to those with early-onset Aplastic Anemia (AA), MDS, or AML in addition to the variable clinical presentations, age at onset also varies and demonstrates anticipation, in which each generation is affected at an earlier age [31,32]. All these features may be explained by differences in baseline telomere length. Each generation inherits shorter telomeres and those with the shortest telomeres are affected at earlier ages and with more severe phenotypes [31,33]. Awareness of anticipation is important because a child inheriting a TERC or TERT mutation could present with clinical manifestations before a parent who carries the same mutation [34].

Discussion and Conclusion

Familial myelodysplastic syndrome and familial leukemias are increasingly becoming more diagnosed. A basic internet search resulted with multiple genetic information companies offering gene panels that test for the ones mentioned before. With high degrees of penetrance and anticipation clinicians need to be suspicious of a germline mutation when either multiple family members develop similar cancers or develop cancers at an unusual age or if a patient develops a second cancer. With a concise history taken on admission, there was already high suspicious of a familial disorder in our patient because of the development of another AML. If the patient could have been tested for these known genes, then more consistent surveillance would have been offered to her beyond the normal amount a patient receives after complete remission. Also, the patient's family, in the patient's case, her two daughters who subsequently developed AML, could have been tested as well and offered screening knowing that they are at high risk. This once again reiterates the need to offer these genetic testing to all patients diagnosed with MDS and leukemias. Let this case serve as a reminder of the importance of such.

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