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Case Report

Co-Occurrence of Platelet Dysfunction, Myeloid Malignancy and IgA Deficiency in a Family with a Novel *RUNX1* Mutation

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Submitted: 06 March 2017

Accepted: 04 April 2017

Published: 06 April 2017

Keywords
- *RUNX1*
- Familial platelet disorder
- MDS
- AML
- IgA deficiency

Abstract

Familial platelet disorder with propensity for myeloid malignancy (FPD/AML), an autosomal dominant disorder associated with mutations in the *RUNX1* gene, is characterized by mild to moderate thrombocytopenia, abnormal platelet function, and an increased risk of developing myeloid malignancy. We describe a pedigree with a novel *RUNX1* mutation in which the prob and presented with mild thrombocytopenia. She had undetectable IgA levels (<5 mg/dL) as did her mother who had died from myelodysplastic syndrome. A germline heterozygous nonsense mutation in exon 7 of the *RUNX1* gene (c.667G>T (pE223X)) was detected on peripheral blood sampling. Her maternal half-brother with a history of celiac disease tested positive for the same mutation. The patient was undergoing in vitro fertilization at the time of diagnosis and a wild-type *RUNX1* embryo was selected for implantation with subsequent delivery of a healthy baby. We contribute a unique finding of IgA deficiency to the clinical phenotype of FPD/AML. This is also the first report of embryo selection being used to prevent inheritance of an autosomal dominant *RUNX1* mutation.

INTRODUCTION

RUNX1 is a member of the RUNX family of transcription factors, which plays an important role in the development and differentiation of hematopoietic cells. [1] Mutations in *RUNX1* can promote leukemogenesis as seen in AML, MDS, and familial syndromes with a predisposition to hematologic malignancies [2,3]. *RUNX1* is also involved in the development and function of the immune system and disruptions in RUNX1 may promote autoimmunity [4,5].

Familial platelet disorder with propensity for myeloid malignancy (FPD/AML) due to inherited *RUNX1* mutations is an autosomal dominant disorder characterized by mild to moderate thrombocytopenia, abnormal platelet function, and an increased risk of developing myeloid malignancies such as acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) [6,7]. In addition to the common manifestations of this syndrome, findings such as eczema and lymphoid malignancies have also been reported [8,9].

Latger-Cannard et al., recently published the largest cohort of individuals with FPD/AML consisting of nine pedigrees with unique *RUNX1* mutations [10]. Most patients had mild to moderate thrombocytopenia and evidence of defective dense granule release. Bone marrow biopsies for seven patients were examined and showed marked dysmegakaryopoiesis. Among these 41 patients, there were no novel clinical features described as part of the FPD/AML phenotype.

We describe a pedigree with a novel *RUNX1* mutation in which the prob and presented with mild thrombocytopenia. Immunoglobulin A deficiency and celiac disease were found in the affected family members that may be related to the *RUNX1* mutation and is a unique feature of this syndrome not previously reported. In addition to the bone marrow features described by Latger-Cannard et al., biopsies in two of our patients showed mild eosinophilia with atypical granulation not previously described.

CASE PRESENTATION

The patient is a 29-year-old Caucasian female who was referred by her primary physician for thrombocytopenia. She had been found to have a platelet count of 81 $x10^9$/L, which was decreased from 90 $x10^9$/L a few months prior. She was first noted to have a similarly low platelet count at the age of ten but this did not prompt referral to a hematologist until it was noted during a fertility workup at the age of 28. The patient reported a lifelong history of easy bruising but no major bleeding problems or need for transfusions. Her mother had presented

to the same hematologist 18 months earlier at the age of 56 years for leukocytosis, anemia, and severe thrombocytopenia. She was known to have had a normal platelet count 18 months prior to presentation but a lifelong history of easy bruising. She had undetectable IgA levels (<5mg/dL). Her bone marrow biopsy suggested an overlap syndrome of Myelodysplastic/ Myeloproliferative Neoplasm. She died of complications related to thrombocytopenia refractory to transfusions and spontaneous cerebellar hemorrhage one month later without having received therapy for the underlying myeloid malignancy. The patient's maternal grandmother and great-uncle had died of acute myelogenous leukemia (Figure 1). One brother from the same parents as the patient is alive and healthy; the other brother of the same mother but different father is alive and healthy except for a history of celiac sprue.

The patient was taking no medications at the time of presentation. Physical examination was notable only for a few healing ecchymoses.

Initial laboratory evaluation showed a white count of 4 x10^3/ mcL with a normal differential, hemoglobin of 14.5 g/dL (MCV 96.1 fL, RDW 12.8%), and platelet count of 84 x10^9/L (MPV 8.6 fL). Absolute reticulocyte count was 93,200. Of note, she was found to have undetectable IgA levels (<5 mg/dL), like her mother, which was confirmed on repeat testing. Given a family history of celiac disease in one brother, tissue transglutaminase IgG and IgA were tested and were not elevated.

Peripheral blood smear showed normal to small size granular platelets, morphologically normal red blood cells, neutrophils with good nuclear segmentation and cytoplasmic granularity and mild eosinophilia. Bone marrow biopsy demonstrated a normocellular marrow (60%) with moderate erythroid hyperplasia, mildly increased megakaryocytes, mild eosinophilia, and no increase in blasts (<5%). Approximately one-third of the megakaryocytes displayed atypical features. These included (in descending order of prevalence): smaller size, increased nuclear: cytoplasmic ratios, decreased nuclear lobation, and/or separate nuclear lobes (Figure 2, A-C). Eosinophils and precursors were mildly increased and included some with coarse basophilic granules (Figure 2B). Interestingly, a similar spectrum of bone marrow morphology was seen in the patient's brother, who did not have thrombocytopenia (Figure 2, D-E). In her mother's

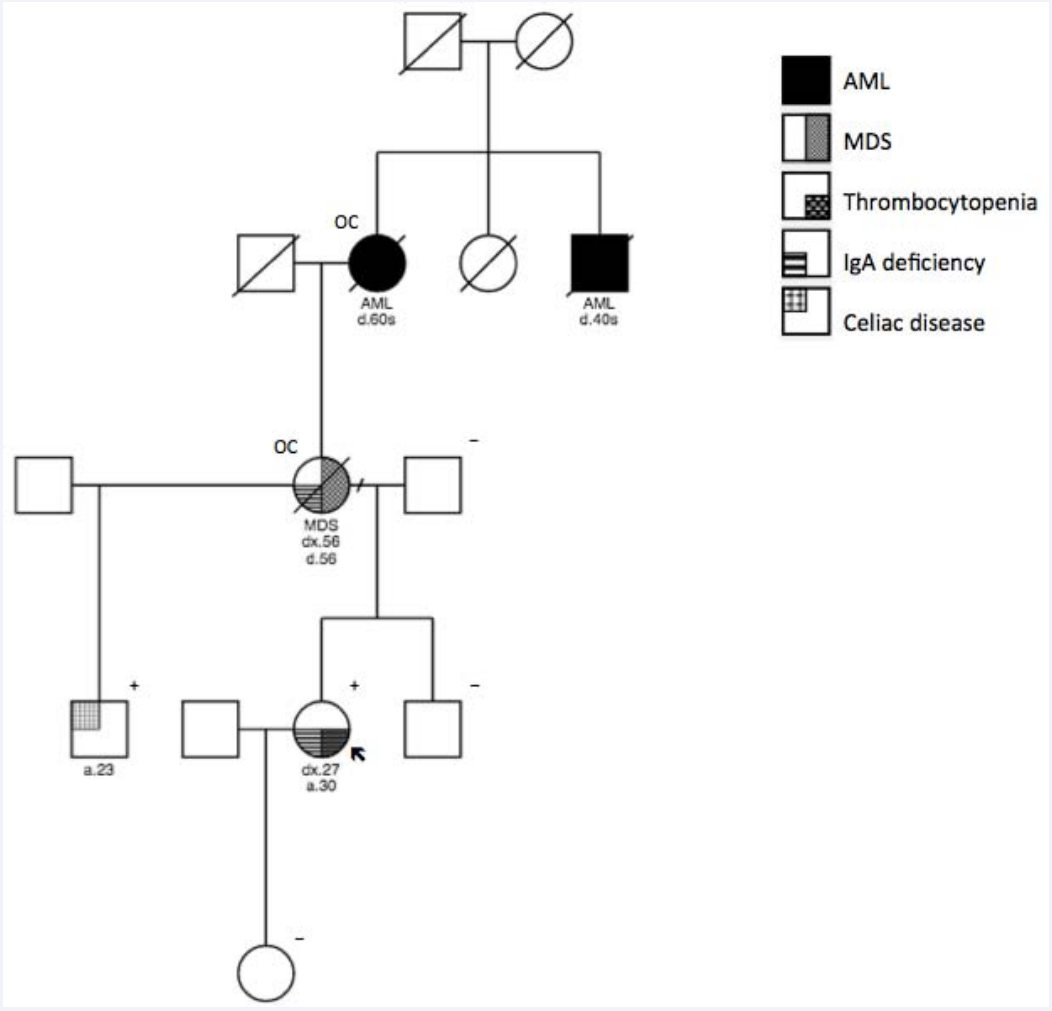

Figure 1 Phenotypic variation in a family with a germline RUNX1 mutation. –, negative for RUNX1 mutation; +, positive for RUNX1 mutation; d, age of death; a, age at last contact; dx, age of diagnosis; OC, obligate carrier; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.

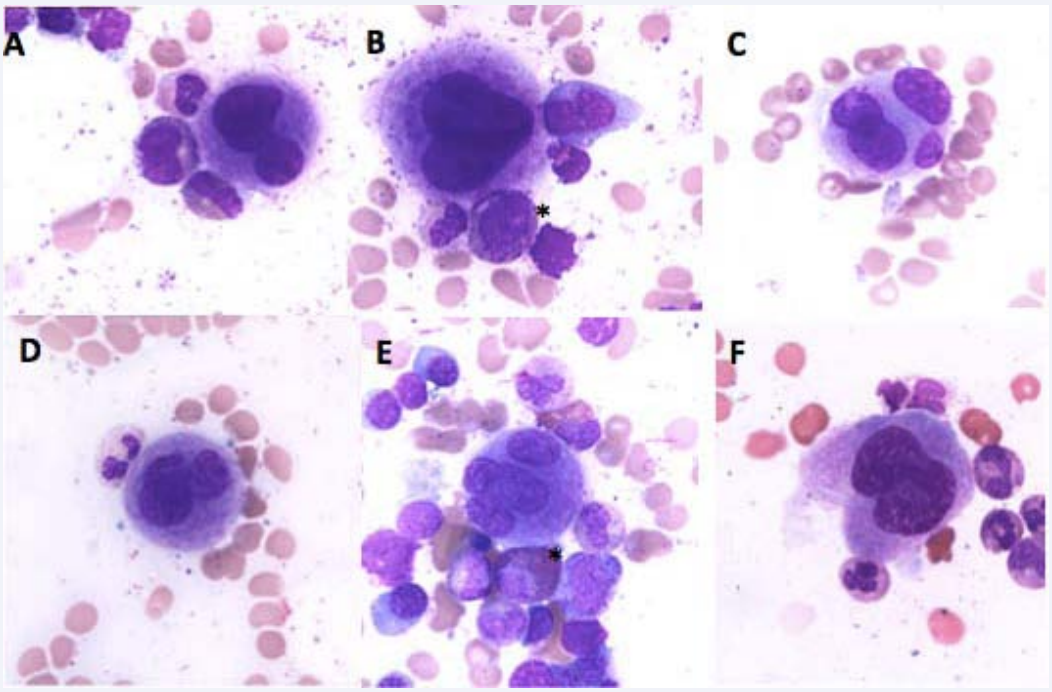

Figure 2 Atypical megakaryocyte morphology on bone marrow aspirate smears. In the patient (A-C), megakaryocytes included frequent small forms with increased nuclear to cytoplasmic ratios and decreased nuclear lobation (A, B) as well as a few forms with separate nuclear lobes (C). The patient's brother (D-E) and mother (F) showed a similar spectrum of atypical megakaryocyte morphology. In addition, eosinophils with coarse basophilic granules were also noted in the patient as well as her brother (B and E, respectively, asterisk). (Wright-Giemsa stain, x1000).

bone marrow biopsy, megakaryocytes were decreased, but again included small forms with high nuclear: cytoplasmic ratios and reduced nuclear lobation (Figure 2F).

Due to the significant family history, molecular testing was done on this patient. A heterozygous mutation in exon 7 of the *RUNX1* gene (c.667G>T (pE223X)) resulting in a premature stop codon was detected on peripheral blood sampling. No mutations were found in *ASXL1, EZH2, ETV6* or *TP53*. Further testing of saliva and buccal specimens demonstrated similar levels of this mutation when compared with the blood, consistent with a germline mutation. Her maternal half-brother with a history of celiac disease also tested positive for the same mutation. Her father and one brother were negative for the *RUNX1* mutation and no specimen from the mother was available for testing.

The patient was undergoing in vitro fertilization at the time of diagnosis. Embryos were frozen after biopsy at day 5/6 of development. Using laser dissection, approximately 5 to 10 cells were removed from the trophoectoderm of each blastocyst for mutational analysis and a *RUNX1* negative embryo was selected for implantation.

During pregnancy, her platelets ranged from 100 to 79 $x10^9$/L but she had no major bleeding problems. In fact, she had resolution of her spontaneous bruising during pregnancy. Platelet function testing during the third trimester showed abnormal platelet aggregation in response to epinephrine. Platelets increased to 105 $x10^9$/L after delivery. She is now 52 weeks status post uncomplicated vaginal delivery of a healthy baby girl.

DISCUSSION

We describe a pedigree with FPD/AML for which mutational testing was done for two patients revealing a novel *RUNX1* mutation. The prob and had thrombocytopenia and platelet dysfunction and her half brother had a normal platelet count and absence of bleeding symptoms. Their mother had a normal platelet count but a history of easy bruising prior to developing MDS. FPD/AML is known to produce a variable phenotype among affected individuals who share the same *RUNX1* mutation and only a proportion of affected members develop AML [11,12]. It may be that significant platelet dysfunction and progression to leukemia develop as a result of the accumulation of additional mutations in *RUNX1* and other genes.

Additionally, this pedigree shows evidence of immune dysfunction including IgA deficiency and celiac disease, neither of which has previously been described in association with FPD/AML. Sorrell et al described a pedigree with a *RUNX1* mutation at the 3-prime end of exon 8 (c.1413_1414insGC (p. L472X)) in which carriers had mild to severe eczema that directly correlated to their degree of thrombocytopenia and/or clinical bleeding difficulties [8]. One report describes a patient with FPD/AML due to a *RUNX1* mutation in exon 8 (c.837G>A (p.W279X) who had a history of recurrent infections during childhood including lower extremity cellulitis, periorbital cellulitis, and perirectal abscess [13]. Similar to our pedigree, mutations in these cases were within the C-terminal region of the RUNX1 gene, which is less common as most *RUNX1* mutations associated with FPD/AML are found within the runt-homology domain near the N-terminus of *RUNX1* [14].

Voon et al., reviewed the role of the *RUNX* complex as a regulator of hematopoiesis and its effects on immune function, particularly their rolein the developmental pathway of many immune effector cells [4]. The *RUNX* proteins are each involved at different stages of B cell differentiation including transforming growth factor beta-mediated IgA class switching [15,16]. The *RUNX* complex is also involved in the differentiation and function of regulatory T cells and disruptions in these proteins are shown to be associated with autoimmune conditions such as systemic lupus erythematosus and psoriasis [17]. Variations in the *RUNX3* locus have been associated with celiac disease and ulcerative colitis [18,19]. Alteration of the *RUNX1* gene may be responsible for both IgA deficiency and celiac disease seen in our pedigree, however there is currently no evidence of a direct link between *RUNX1* mutations and these entities. This may be a potential area for further study.

Latger –Cannard et al., described the bone marrow features of seven patients with FPD/AML. Biopsy specimens showed dysmegakaryopoiesis with hypolobulated or immature megakaryocytes with high nucleo-cytoplasmic ratio, strongly basophilic cytoplasm, and poorly lobulated nuclei in association with micromegakaryocytes [10]. These findings were consistent with those seen in our pedigree. In addition to megakaryocyte abnormalities, bone marrow biopsies for two patients in our pedigree show increased eosinophils with atypical basophilic granulation (Figure 2).

In conclusion, we contribute to the literature a report of a novel mutation in a FPD/AML pedigree with unique features of the bone marrow histology and clinical phenotype. This is also the first report of embryo selection being used to prevent inheritance of an autosomal dominant *RUNX1* mutation. We hope these findings will improve the ability of clinicians and pathologists to recognize this entity.

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Cite this article

O'Neill C, Siddiqi I, Gruber S, McDonnell K, Moayeri S, et al. (2017) Co-Occurrence of Platelet Dysfunction, Myeloid Malignancy and IgA Deficiency in a Family with a Novel RUNX1 Mutation. JSM Bone Marrow Res 1(1): 1004.